EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

MEETING REPORT

NOW-CASTING AND SHORT-TERM FORECASTING DURING INFLUENZA PANDEMICS

A focused developmental ECDC workshop

Stockholm, 29–30 November 2007

ecdc.europa.eu

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SUMMARY: RECOMMENDED ACTIONS TO BE TAKEN

The meeting/workshop was very successful. Thanks were expressed to all those who prepared and presented their work. Recommended actions to be taken included:

- preparation of a list about what data to collect — and with which rationale. The list would be quickly constructed and taken to the December WHO 'Surveillance in a Pandemic' Workshop (Netherlands and ECDC);
- organisation of a Europe-wide meeting, repeating some of the content but focusing on the possible use by more countries of the UK First Few 100 database. This was recommended to take place in the first half of 2008. To be coordinated by ECDC;
- in anticipation of the needs of the Flu Section of the Health Security Committee, there should be meetings in 2008 to review the scientific evidence on border closures and school closures. One of these (probably the one on school closures) could be coordinated by one expert, the other one by ECDC, but both have to involve several expert centres; and
- it was essentially agreed to promote access to all data for modelling, not only epidemiological parameters.

BACKGROUND

One of the difficulties identified in the ECDC 'Surveillance in a Pandemic' working document is the pressure on those people responsible for public health and surveillance to come up with 'real-time' estimates of what is happening during a pandemic. Specifically, there are major difficulties in producing regular and accurate estimates of the numbers of people that:

- are infected with the pandemic strain;
- require care (including antivirals) because of influenza;
- need hospital care; and
- are dying.

These difficulties have a variety of reasons, including the expectations of decision makers, media requirements and expectations, as well as managing rumours ('many people are dying from flu, flooding the hospitals in Region X'), etc.

In addition, there are management requirements like anticipating needs and pressures on services in the immediate future, so that resources can be moved around inside countries and strategies can be changed, e.g. if it appears that anti-viral or antibiotic stocks will be running low before the end of the pandemic wave, or that hospitals will soon reach capacity in a particular location.

However, the difficulty is that the sort of surveillance information that is expected or required — specific infection rates, latency periods, additional hospitalisation and death rates,

attributable to influenza — is rarely immediately available even under normal circumstances[1], let alone under the stresses and strains of a pandemic (see ECDC *Surveillance in a Pandemic* working document).

A POSSIBLE SOLUTION

One of the potential ways that could overcome some of these difficulties is to use real-time influenza modelling adjusted by a) assumptions about the behaviour of the new pandemic strain and b) available surveillance and monitoring data. There are some organisations in the UK that are trying this approach in order to provide what has been called 'now-casting' and 'immediate forecasting'. This approach was used with some success in the 2007 Winter Willow Exercise where ECDC and the European Commission acted as both players and observers.

In brief, the concept calls for modellers used to working with surveillance data. These modellers will run a real-time model that provides numbers on estimated current and short-term future infections, people requiring primary care, people needing hospitalisations, people requiring anti-virals, death cases etc. This could be run on a daily basis as part of the surveillance activity, sub-divided by broad geographical regions inside a country. The model, its assumptions, parameters and hence its outputs could then also be adjusted and updated at the national and local level, according to independent surveillance and monitoring indicators: sentinel data, reports of antiviral usage, hospital bed use, etc. The now-casting outputs might then be distributed to the decision makers and published on a regular basis clearly labelled as 'modelling estimates'. The forecasting outputs would be used to inform decision makers as to likely scenarios for the rest of the wave with particular emphasis on when maximum service levels will be exceeded, supplies will be insufficient, etc.

As this stage, this is merely a concept, rather than a working model, and the UK work is not all that advanced. To develop the idea further, ECDC invited a small number of groups of modelling and surveillance specialists to a small workshop in Stockholm where the main presentation will be from the UK. The UK group will present their current work to four pairs of influenza modelling and surveillance specialists from other countries. Numbers of countries are deliberately limited and were selected from a list of countries where modelling and surveillance specialists have a relatively strong tradition of working together. The ministries of the respective countries will be informed of the event, as they are usually the customers of the development.

[1] Exceptions to this generalisation are some primary care sentinel data for influenza like illness or acute respiratory infection though national systems reporting to the European Influenza Surveillance Scheme (EISS, www.eiss.org), and its not clear how these will function in a pandemic.

Objectives

The objectives are

- to learn about the UK approach, including their method of gathering initial data for the assumptions; their strengths, weaknesses, and the experience during Winter Willow;
- to see whether there are other similar or alternative approaches in other European countries and to compare any such approaches to the UK approach;
- to determine whether countries are interested in developing the approach further — individually or collectively — and whether ECDC should hold a larger workshop;
- to determine to what extent now-casting and short-term forecasting is possible with currently available surveillance data;
- to initiate discussion about the validity and improvement of using current mathematical models on the spread of infectious diseases for now-forecasting; and
- to discuss the added value of observing more parameters versus improving data quality of the existing surveillance deliverables. Which data are most crucial to have non-delayed reporting on, in order to deliver forecasts based on very few input parameters?

Outcomes

Expected outcomes were identified as follows:

- a short report on the UK approach and other similar developments in other EU countries;
- a decision on whether to advance this work;
- identification of further specific work needed, and an agreement on who will do it;
- a plan for a second workshop and/or a larger workshop drawing attention of this initiative to other interested parties; and
- information on other work done elsewhere, e.g. by WHO, CDC (USA), etc.

At this initial stage, the workshop would be aimed at countries which both are:

- anticipating producing real-time estimates of infections, people requiring care; and
- already have a close working relationship between modelling and surveillance specialists.

Depending on the output of the workshop, there would later be another meeting or communication to make the results available to all EU/EEA countries .

EXPERT PRESENTATIONS

Peter Grove: Presentation of now-casting techniques

(For presentation please see Annex I)

- Introduction to the history of past pandemics in the 20th century. For identifying the range of past clinical attack rates, comparison US and UK data has been conducted.

Attack rates shown to be at least 35%. In contrast, the calculated R_0 values claim higher attack rates.

- For London, 50% higher peak than the national peak. It was suggested to look at epidemics on local level. In the UK it would mean on county level. Calculations performed by Imperial College suggest even a higher number than 50% on local level.
- For the UK, modelling CFRs in the range of 0.4 - 2% are used, based on data from previous pandemics.
- For advised planning assumptions, up to 50% of the population will be ill, serological confirmation for 80-85% of reported cases.
- Case hospitalisation demand rates range between 0.55% - 4%.
- Countermeasures for delaying the peak, utilises an antiviral stockpile covering 25% of the population. This will increase to 50%. Possible use of antibiotics with bacterial complications is included in the modelling work.
- Delivery of antivirals will be telephone-based. Acquaintances will collect the antivirals, delivery to homes possible in exceptional cases.
- School closure protects children, but not much effect on the epidemic. In the current modelling work, antivirals for 35% of the population is assumed. Question aiming at changing antiviral strategy was communicated. School closure protects children, but not much effect on the epidemic.
- For a severe form of virus with CFR exceeding 3%, closing of schools, public events and travel restrictions are implemented.

The situation in other countries:

Sweden

Need to accept uncertainty in doing forecasting. Sweden has considered both a mild and a severe scenario. Effect of antivirals and their distribution is addressed. During modelling, main question is how to keep the community running. Major actors involved to identify activities in the need to be operational during crisis. One option is moving people around in the system. Key persons to be protected with antivirals. Swedish health system is very decentralised, all have their own plans. National board of Health is planning to produce a computer program for predicting the size of a pandemic. The program will be emphasising the possibility of different scenarios.

France

Review of possible strategies of antivirals, prophylaxis to be received at GPs. Distribution of drugs through normal channels. Health care will provide hospitalisation for the very sick, extra places will be made available. Decision has already been made to close schools but some experts want politicians to review this decision.

Netherlands

GPs have a committee discussing pandemic situations. No antibiotics and antivirals recommended at the moment due to resistance. Current size of antiviral stockpiles is up to one third of the population. Modelling input received from RIVM group of modellers.

Italy

Antivirals are stockpiled and cover one tenth of the population. Modellers are involved in decision making. Modelling intended to estimate the impact of vaccination, antivirals and closing schools.

Question was raised about how the modellers are organised in United Kingdom, considering Health Protection Agency (HPA), Imperial College and other groups. How are recommendations followed from simulations and how much is implemented by the Department of Health? Officials inform ministers of the outcomes. Main focus on several results from different group of modellers, HPA produces 'simple models', Imperial College very complicated ones. Focus on whether the results are same or different between the outcomes. HPA has one back-up group of modellers in case the first one is incapacitated.

Arlene Reynolds: Overview of UK surveillance — data sources, limitation and reporting systems

(For presentation please see Annex II)

- Reliability of the UK surveillance system during a pandemic; data can be gathered at regional level. Used for estimating the number of cases, deaths and for measuring how health care facilities are coping with the outbreak. Communication with media is of importance. Existing systems on influenza are running. HPA acts as WHO reference laboratory. The surveillance system monitors a number of sources, like sentinel GP schemes and GP incidence rate for influenza. QFlu monitors number of GP consultations, covers approximately 20% of the population. PCT 130 000, on weekly basis during pandemic on daily basis.
- Possibility for data overload problems during a pandemic. The audience agreed that this is the situation with many surveillance systems during a pandemic.
- A publication about primary care capacity in UK is in progress, to be published in Eurosurveillance.
- An issue with QFlu is that it needs many sources. No follow up on some data. NHS winter pressure during non-pandemic flu season to be investigated. Acute trusts exists for rapid actions.
- Secondary care more qualitative, acute trusts exist, not harmonised data, not specific to flu, represents severe end of spectrum.
- Mortality data is available on weekly basis, reports total number of deaths. In the system, 2–3 week delay on reporting to get correct data. A pilot study conducted at the Emergency Department was made to assess the delay.

Mortality reporting system in other countries:

France

Specific influenza mortality surveillance based on a sentinel system. Sex, age and place of death is reported after 10 days.

Daily number of deaths (without the cause of death), 90% reported within 7 days.

Netherlands

Daily number of deaths after four days.

UK

Data from registration, 80% reported within five days.

Italy

Sentinel system in 21 cities. Previous months' deaths reported on the tenth of the preceding month.

- A First Few 100 (FF100) database for complications, symptoms for cases, record what happens with people with flu, and follow up including possible contacts. The database is to provide information to estimate epidemiological parameters for forecasting. Testing during normal flu season for forecasting, has not yet been implemented.

The following points were raised after the presentation:

Question raised about the sensitivity of sentinel systems with data from multiple sources. A paper published about clinical prioritizing, how to deal with symptomatic cases. Problem arises when outside normal working hours (9 to 5).

What are the possibilities for adding an internet-based system? This has been addressed, but it is important to know the properties of different systems.

Peter Grove: From data to information

(For presentation please see Annex III)

- For forecasting, UK uses two modelling approaches and three different teams. Daily telephone meetings are conducted. Incoming data includes ILI. Antivirals authorised to aged persons and for possible complications. GPs report complications. Plan includes distribution of antivirals to children under three years. Data on hospitalisations are reported as well.
- Information to policy makers includes forecasted modelled numbers, a now-casting estimate, and estimations of previous weeks. Factual information reported separately and with time stamp. Data will be provided on region and age.

Steve Leach: Pandemic influenza: a beginning to epidemic forecasting

(For presentation please see Annex IV)

- Why do we need real-time models? Leach et al. have re-analysed the data from three previous pandemics, modelled on a weekly basis, with 10 parameters. Another model showed the big uncertainty on spatial scale when flu is imported to UK. It is impossible to know how it is spreading, although it is more likely to come through entry points, with large number of people transferring through.

- In addition to the UK data, it is important to have same data for all groups. HPA takes the lead in organising this. 1 in 5 symptomatic cases report to GPs, and 50% cases are asymptomatic.

The following points were raised after the presentation:

Question from EISS: How will EISS be used during a pandemic? Availability of data needed for the kind of modelling shown by Leach.

It is very difficult to model flu spatially, we will not know how it develops and we should be careful when producing animated maps. On the regional level, we might predict what a regional outbreak might look like, noted Åke Svensson.

Simon Cauchemez: Statistics for the real-time monitoring of a pandemic

(For presentation please see Annex V)

- Necessary key indicators for surveillance, for estimating basic epidemiological parameters.
- In data collection, effects of underreporting, report delays and possible sampling bias can affect the calculations.
- Real-time modelling, using data from SARS outbreak. Data was available on CFR; problem that CFR depended on raw data.
- Also not observing incubation time completely, calls for methods to account for truncated data, from survival analysis.
- Showed methods to account for sampling bias based on follow up of households for estimating epidemiological parameters. Raised the question on what kind of data will actually be collected during a pandemic.
- There are several statistical issues in addition to the sampling effects, especially what happens at the beginning. A major concern is the use of non-real time data, we do not know exactly what data was available on different days. Need to recalculate, with reference to delay of data reporting.

The following points were raised after the presentation:

Worries on uncertainty assumptions in the shown model, addressed by Åke Svensson.

Peter Grove: Presentation of exercise 'Winter Willow'

(For presentation please see Annex VI)

- In policy making, information exchange is very often flawed. Need to define who contacts whom. Important lessons learned about whom to contact 'higher up' in the hierarchy, specially when trying to avoid 'Chinese whispers'.

The following points were raised after the presentation:

In the Netherlands, the decision making process is simpler than in the UK. RIVM is involved in many steps and is consulted by the department of health. Most capacity in UK seems to be at HPA.

John Paget: Currently available epidemiological and virological surveillance data: European Influenza Surveillance Scheme 1996–2007

(For presentation please see Annex VII)

- EISS has access to data at the European level. It covers 35 European countries, more than the number of EU Member States. Collects ILI/ARI rates by week and age group. Produces an intensity indicator. Plots geographical spread by week. EISS has access to virological data.
- A study analyzing data on influenza season length and spread at the European level was presented. Eight seasons are covered, a west-to-east spread occurred four times. Analysis with mortality data, data with monthly detail. The observed maximum duration of the peak is limited to four weeks a year.

The following points were raised after the presentation:

- Important to know what to expect from the analysis of spatial spread. Different patterns are caused by different predominant viruses.
- Need to differentiate between years with high and low incidence rates.
- A study in relation to climatic variables could enlighten the results further. London School of Hygiene and Tropical Medicine is performing a study on this and flu activity. Burden of disease should be addressed as well. There is a module on the EISS server to perform this.
- Question regarding the sentinel system; much depends on GP consultation rates, these differ between countries, e.g. differences exist between UK and France sentinel data. Countries do report age groups differently.

Jacco Wallinga: Real-time modelling and estimation of time-varying variables

(For presentation please see Annex VIII)

- Real-time modelling is needed but has to rely on a number of assumptions. In order to get 'realistic' values suited for a number of estimates, a panel of experts can be used.
- Modelling might yield some non-linear results; conducting a sensitivity analysis is not always straightforward. Indeterminacy does not lead to the best model structure and an optimal set of parameter values when using available data.
- Researchers should use at least two models to see the model behaviour.
- Researchers have to concentrate on the data requirements for modelling and on optimising control policies.

- Not only epidemiological parameters like R_0 are of interest for modelling, data access is crucial because different models can provide different R_0 with the same data.
- Illustration of a method necessary, calculation of the number of secondary cases using infection trees. Data included:
  - case ID;
  - date of symptom onset;
  - ID of most likely infector;
  - group membership;
  - size of population at risk; and
  - group/specific infectivity.

The following points were raised after the presentation:

Sensitivity in model structures, effect of comparison of different FF100 databases.

Difference between models is an extremely important issue, addressing model comparison methods. How to compare simple models versus very complex models? In the Netherlands, only very few complex models are used. Question raised about running the same models at many institutes at the same time. Note by Jacco Wallinga: there is added value in having many different models.

Idea about creating a PCR test during a pandemic. Comparison with the past H7N2 outbreak. It turned out to be difficult to do serology, Nick Phin noted. Creating a PCR test is not commercially interesting. Need to set up and promote research interest.

Hanna Merk: Population-based surveillance of influenza

(For presentation please see Annex IX)

- Population-based surveillance of influenza. Traditionally performed in Sweden by sentinel and laboratory reporting. Problems during Christmas period, as number of reporters goes down.
- Sentinel and laboratory show different things. Laboratory reporting much higher than sentinel, specially for the age-group 65+.
- Different methods to estimate burden of disease in the community; telephone survey conducted covering one week. The study showed 3.6% ILI in the community, while sentinel systems predicted 1% ILI.
- Other methods involved actively contacting participants. SMS, IVR and telephone interviews conducted. Researchers made calls during five week days.
- New pilot study, IVR or web. This can be seen close to real-time surveillance. Evaluate contact modes and investigate the compliance.

The following points were raised after the presentation:

Would it be possible to do a testing of a sample? Patients could be tested with strips which are mailed. Note from Angus Nicoll: Why do we need this if our sentinel surveillance works? In Sweden people do not go to the GP very often and therefore will not be reported by the sentinel system.

It was mentioned that this study could be related to a burden of disease study. If you see a case, this might represent a proportion of people. How do countries differ in the way health care professionals report? What happens in Sweden when something happens? Sentinel systems are designed for hospital communication and not intended as preparedness tools. Note from Angus Nicoll: need for a joint European network for burden of disease during a normal flu season.

Burden of disease is a way of identifying people within this system, and assigning a unique ID number prevents repeated reporting of the same person. In UK: need to monitor flu activity and determine threshold value when antivirals can be distributed. Note by Nick Phin: Used ideally for alerting hospitals; we need to know the surveillance system properties. A Japanese study about the use of antivirals in hospitals is published.

Internet-based surveillance systems might be the future of flu surveillance and reporting. What are the differences between an internet-based and a traditional surveillance system? Note by Jacco Wallinga: Much uncertainty exists about internet-based reporting; different things are reported, different groups are covered. A study comparing non-responses with EISS could be performed. A possible bias is introduced by media attention, followed by a temporary increase in internet reporting.

One problem is that one system will not solve all problems. Unsolved questions of robustness of different systems remain.

When does a patient have to see a GP for a medical certificate? In Belgium, it is after one day of sick leave, in Sweden it is three days; these rules can bias the sentinel reporting in different countries.

Pierre-Yves Boelle: A 'small-world-like' model for influenza pandemics: structure and intended use

(For presentation please see Annex X)

- Individual-based model for influenza.
- Model incorporates time-varying infectiousness after infection.
- Susceptibility in the population is varying with age. Based on studies performed in France.
- Different assumptions on the population, mixing weekdays and weekends.
- 90% of the cases assumed to have sought medical advice.

The following points were raised after the presentation:

Need to address issues such as assumptions and comparability of models. Which assumptions are important and how do these affect the results? Model should not be seen as a fixed entity, comparisons between models become a big issue.

Note by Steve Leach: What about travel restrictions, uncertainties and assumptions on parameters in this model? These vary a lot. This is rather policy-making ahead of time than real-time modelling. Also, the model is not fitted to actual data.

WHAT CAN BE ESTIMATED AT THE BEGINNING OF AN OUTBREAK?

Epidemiological parameters necessary for modelling can — at best — be estimated after two or three weeks. These can be R_0 and the generation time. Having access to data from Southeast Asia can help in planning for actions in Europe.

A quick list with parameters that can be deduced from collected data was suggested. A first draft of this is in Attachment 1.

Having access to weekly attack rates is of added value. For the 1918 outbreak, there was a discernable difference between different groups dying in different waves. One issue to address is what is more important: the overall attack rates for risk groups or the question which risk groups show the most transmissions. There is added value in designing household studies in order to estimate transmission between groups. A lot of data has already been analyzed. We might get data collections from Thailand, cases and links. If a person is infected by a child, it leads to children getting rated as more infectious than adults. This may be true for a population with just kids but in a real population this is not true.

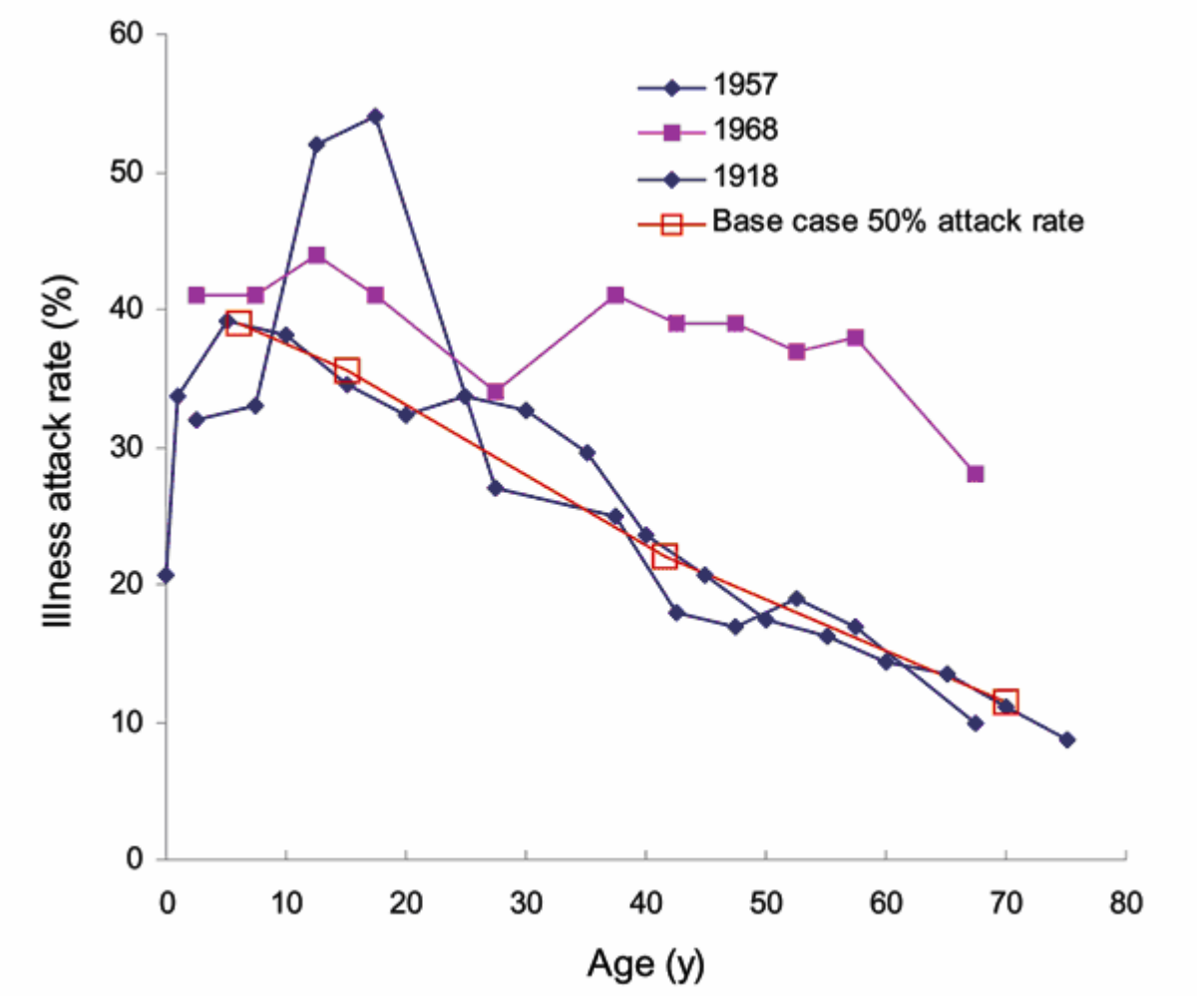
It is important to notice that reported values on epidemiological parameters, such as R_0 and the generation time, is not sufficient for performing modelling. Modellers need access to the raw data, so they can make their own estimates, fitting their model of choice. As addressed in Jacco Wallinga's presentation, identical data can result in different estimates on the epidemiological parameters. This data should be made publicly available to all who want to use it, without any delays.

Note by John Paget: For WHO, we need to demonstrate a data-transfer mechanism. How can systems work during a crisis situation? In a pandemic situation, some systems might still be working very well. For H5N1 in Turkey, WHO was involved, and no legal regulation was in place.

Question raised about WHO's mission for modelling. It was suggested that this meeting will provide advice on what data to collect. Discussion if two lists are needed, one for Europe and one for WHO to be used on a global scale. There might be major differences in data availability and requirements. What age groups, what types of groups? What is the burden of illness in risk groups? Is it feasible to do studies at the community level? Thailand has managed to conduct studies at the community level.

DISCUSSION ON NONPHARMACEUTICAL COUNTERMEASURES

Graph discussed during the meeting: Glass RJ, Glass LM, Beyeler WE, Min HJ. Targeted social distancing design for pandemic influenza. Emerg Infect Dis. 2006, 12(11):1671–81.



If the pandemic behaves like during 1957, closing schools would be effective, although New York data is not suggesting that.

Modelling results from Imperial show that school closure has no major impact on the cumulative attack rate, although it might impact on the timing of the peak. These results depend on assumptions of how school children are mixing. The most probable explanation for this result is that the Imperial College study underestimates the effect of children's contribution to the spread of disease.

Questions were raised concerning the timing of school closures, where uncertainties remain because of insufficient or old data. This makes school closure modelling results difficult to interpret. Do the data reflect a seasonal or a pandemic period?

There was concern whether the graph shows data collected over a week or whether it covers the entire study period. Further clarification is needed on the relation between transmission

and age group. To which extent are the children part of the outbreak? We need to look at the transmission pattern and conduct a study on transmission patterns.

The closing of schools might continue when there are signs of a severe pandemic. Closing schools at the beginning of a pandemic means that the peak will be delayed. Closing schools close to the peak will effect the attack rate. Scientific evidence is low on what actually happens at the peak. There are good reasons for closing schools if young children are at risk to become seriously ill. There are differences when designing and running models. Can a model based on data from 1957 (with school closure) be effective?

The 1968 epidemic assumptions are made at HPA. But the HPA models are run on seasonal influenza and based on data from the Christmas period, so it remains unclear how this can be used in real-life situations.

In a pandemic, we need real-time modelling to see which of the shown attack rate curves we are in. On the left hand side of the figure, the age groups under thirty show the most discrepancies. At the end of the epidemic, the older age groups looks the same in all curves. For 1957, all major shifts are at right hand side, with mostly elderly persons involved. This graph does not provide any suggestions on the severity of the disease. WHO suggests monitoring intensity should be indicated.

COMMUNICATION WITH POLICYMAKERS ABOUT COUNTERMEASURES

Decisions have to be taken in France and the UK, who tend to close schools at the start of a pandemic. This is a highly political context, and the threshold has to be decided on. The 2007–2008 season in Australia resulted in five to six deaths in children, although seasonal activity was extremely low. Decision makers tried very hard to be media-friendly.

Sweden ran a pandemic simulation to test administration functionality, trying to determine how to act during the peak.

There is the possibility of using interfaces for policymaking. But if policymakers are not aware of the limitations of the interface's model, it is probably not helpful for policymakers to run the interface. What can be done to make them run the model and see the effects? Should schools be closed, or should they stay open while the children receive antivirals? What is more effective? These question will be asked, and advice will be expected from the interface.

In most EU countries, policymakers are not connected to modelling outputs. There are differences in policy making, caused by internal dynamics and regional uncertainties about what to do. 'Winter Willow' showed the possibilities to move antivirals within a country. When the south was affected before the north, policymakers in the north did not want to move antivirals to the south. Another exercise at the European level yielded similar results.

POSSIBLE CONTINUATION OF THIS MEETING

It was agreed that presentations given at this meeting could be published, possibly after the removal of some sensitive parts.

One issue was to compare national capacities against capacities at the European level. Access to data at the European level is important. How willing are countries to share data? There is no experience in this field. If one country is hit first, data sharing possibilities depend very much on which country it is. There is a real need to demonstrate data sharing. This would be even more convincing if data from a real outbreak could be provided. One possibility would be to test this during a normal 'seasonal' flu season. First, it should be investigated which countries have similar databases. Is there any experience in data sharing? During a pandemic, the first recorded cases might be from a normal flu. ECDC should take the lead and arrange a meeting in 2008, inviting Member States to test some existing data-collection databases such as FF100, show/share their own experience and solutions. Disseminating now-casting experience would be useful at a meeting of this kind. The participants agreed that there was added value in getting data on FF100 for all of Europe. It is still unclear how we can interpolate from the FF100 database to cover entire populations. Modelling performed should be based on data from all countries.

Will it be necessary to construct similar databases for other diseases? Will some countries adaopt the model and start using it?

During the discussion, border closures were mentioned. Closing borders would, at least potentially, limit access to antivirals from abroad. HSC has a 'flusection' subgroup. ECDC hopes to have discussions with more senior people in this group, which would provide an opportunity to discuss topics on a higher level. The results of border closure simulations will probably be followed by countries with no own modelling capacity. It would be worthwhile to bring together leading modellers so they can discuss critical parameters and models needed for border closure simulations. As a final result, country-specific answers should be available, which would probably require more than just one meeting. At the European level, some kind of EU-level action plan needs to be put together on this issue. It was mentioned that border controls were basically implemented to prevent infection moving from coming to country. Yet access to antivirals from other countries remains a key question in border closures. People might travel more to other countries, trying to get access to antivirals. In this context, we need to define the meaning of border closures. Also, panic in the communities might rise due to H5N1.

The effects of school closures are not always thoroughly analysed. It was agreed that epidemiological analysis is also needed for the negative effects of school closures. How will this effect everyday life? ECDC should take a leading part in arranging a meeting to draw on the work done on school closures. One issue are the legal instruments in different countries to impose school closures. One example is a survey during the G8 meeting: 'What is your policy during a pandemic regarding airports?'. There are marked differences in how countries react. It is essential to get HSC's 'flusection' subgroup to include these topics in their work

plan. One area are the effects of school closures. Participants voiced different views on school closures. The UK wants to close schools to get R_0 near 1, the Netherlands close schools at the peak. Surveys should be made on what impact these approaches have on the communities. There is also a need having a health economist onboard. In Italy, preliminary modelling results show that school closures are not very useful, but are effective in delaying the epidemic peak. This is not widely discussed with the policymakers. In France, there is not much discussions yet. The government point of view is that schools will be closed.

In scientific studies, border closures have not be shown to be effective. Border closures might be implemented simply to show that something is being done. However, the question remains for how long borders can be closed. The UK can pass 10 days before it needs to import food. Only a meeting at a higher political level can address the issue of why, or whether, we need to close borders. This should be coordinated by an expert centre, or, rather, by several centres. One centre can coordinate this activity, but input is needed from several centres.

As to modelling, challenges at the European level were addressed. Also, the comparability of data needs to be resolved, an issue that also affects EISS. EISS has more data on the signal, while modellers would prefer data from virological confirmations. Virological data at the European level is extremely difficult to get hold of. This issue should be tackled at the upcoming DG Research FluModCont project.

Statistical problems were addressed, especially surveillance during pandemics. How should changes in the surveillance systems be planned? Information on. In order to gain real-time information on the possible effects of intervention, access to surveillance data is needed.

Additionally, work needs to be done on serological tests. This can be performed by one or two different centres. Samples need to be sent to these places. Funding for testing of samples might be possible through public health programs. One concern is that this approach will tie up a lot of resources. It was concluded that serological work needs to be done at a fixed location. It would be much harder to distribute a serological test.

ATTACHMENT 1: WHAT TO COLLECT LIST

There are several variables to estimate during a pandemic.

These variables can be divided into two main groups:

- For clinical use:
  - burden of illness;
  - clinical attack rates (risk of infection, risk of disease);
  - proportion of infections showing clinical symptoms; and
  - severity of disease (case fatality rate).
- For decision support (modelling):
  - reproduction number (basic and effective);
  - generation interval (mean, distribution);
  - epidemic curve with daily number of new cases (attack rate per day, per week…);
  - infection attack rates (serology); and
  - burden of illness -> to estimate groups.

These variables are to be estimated from existing data (both historical and incoming data). The estimation process inherently involves models of varying kinds for inference, and using the same data might result in different values and similar predictions. Therefore, the mere communication of estimated values is not helpful; depending on the model structure used, different estimates can be given. Communication and the sharing of data is essential.

The data have to be collected:

- at the individual level:
  - case ID;
  - date of symptom onset and how reported;
  - ID of most likely infector(s);
  - name of hospital if hospitalised; and
  - group membership (age, sex, occupation).
- at the population level:
  - population at risk;
  - size of groups in population;
  - number of susceptible in groups in population;
  - number of individuals with defined symptoms;
  - number hospitalised;
  - number of deaths.

Serological testing/cross-sectional serological surveys should be initiated.

Epidemiologically designed household studies should be initiated when possible. This approach can reduce bias in the collected data.

ATTACHMENT 2: PARTICIPANT LIST

Nick Phin	Health Protection Agency, Centre for Infections, UK
Steve Leach	Health Protection Agency, Porton Down, UK
Arlene Reynolds	Department of Health, UK
Peter Grove	Department of Health, UK
Simon Cauchemez	Imperial College, United Kingdom
Cristina Rota	ISS, Italy
Marianne van der Sande	RIVM, The Netherlands
Jacco Wallinga	RIVM, The Netherlands
Isabelle Bonmarin	InVS, France
Pierre-Yves Boelle	Jussieu, University 7, France
Hanna Merk	Swedish Institute for Infectious Disease Control, Sweden
Åke Svensson	Stockholm University, Sweden
Anders Tegnell	National Board of Health, Sweden
John Paget	European Influenza Surveillance Scheme, The Netherlands
Nikolaos Stilianakis	Joint Research Centre, Italy
Bruno Ciancio	European Centre for Disease Prevention and Control
Angus Nicoll	European Centre for Disease Prevention and Control
Tommi Asikainen	European Centre for Disease Prevention and Control
Howard Needham	European Centre for Disease Prevention and Control

Apologies

John F. Ryan	DG Sanco, European Commission
Franz Karcher	DG Sanco, European Commission
Karoline Fernandez de la Hoz	European Centre for Disease Prevention and Control
Roberta Andragetti	WHO Euro
Caroline Brown	WHO Euro
Gianpaolo Scalia-Tomba	University Tor-Vergata, Rome, Italy
Ben Cooper	Health Protection Agency, Centre for Infections, UK

ATTACHMENT 3: SCHEDULE

Day 1

11:30 – 13:00	Lunch and arrival at ECDC
13:00 – 13:15	Introduction
	Welcome, presentation of ECDC, introduction, presentation of the background and needs of this workshop. Presentation of terminology, real-time modelling, now-casting and short-term forecasting.
13:15 – 13:30	Reimbursement information, Missions and Meetings department ECDC
Presentations from participants	
13:30 – 15:30	UK Session (schedule distributed separately)
15:30 – 16:00	Peter Grove, Arlene Reynolds, Nick Phin, Steve Leach, Ben Cooper, Simon Cauchemez
Afternoon tea	
16:00 – 16:20	John Paget, Currently available epidemiological and virological surveillance data: European Influenza Surveillance Scheme 1996–2007
16:20 – 16:40	Hanna Merk, Population-based surveillance of influenza.
16:40 – 17:00	Jacco Wallinga, Real-time modelling and estimation of time-varying epidemiological variables
17:00 – 17:20	Pierre-Yves Boelle, A computational model for pandemic mitigation in France: structure and intended use
17:20 – 17:30	Summary of Day 1. Introduction of work for Day 2, Tommi Asikainen, Angus Nicoll
19:00 – bedtime	Dinner

Day2

09:00 – 10:00	Modelling specific topics: Discuss the validity of using current models when applied for real-time modelling. What is needed to improve them? Are the methods understandable? What is the minimum information required? Identify gaps in knowledge.
10:00 – 10:30	Surveillance specific topics: Discuss the current surveillance systems. What are the time-delays on reporting? Possibilities to change reporting; what information can be gathered? Is it possible to gather

	more observations when reporting cases? Is gathering more information from some cases a surveillance objective/task? What are the differences/equalities between surveillance systems in different countries? Do we survey the entire population or only some specific groups (sentinel system)?
10:30 – 10:50	Coffee break
10:50 – 11:20	Continuation of surveillance specific topics
	Public health and policymaking viewpoints. Bearing in mind the discussions over the past days, is there added value for policymakers to use real-time modelling?
	To what extent should this be done? Will modellers and surveillance specialists just report their predictions, and how important is it to know and communicate the assumptions, uncertainties and limitations about these?
	Is there a need to do more research on modelling and surveillance? What about interaction with policymakers? This is a tricky issue since researchers always want money. Can the extra expenditure be justified by its public health impact?
11:20 – 12:30	Summary
12:30 – 12:45	Rounding off both days, Tommi Asikainen, Angus Nicoll
12:45 – 13:45	Lunch
13:45 –	Trip back home

ATTACHMENT 4: ABBREVIATIONS

ARI	Acute Respiratory tract Illness
CDC	Centre for Disease Control and Prevention
CFR	Case Fatality Rate
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
GP	General Practitioner
HSC	Health Security Committee
ILI	Influenza Like Illness
IVR	Interactive Voice Response
NHS	National Health Service
PCT	Primary Care Trust
QFlu	UK based database for flu
WHO	World Health Organization

ANNEX I – ANNEX X: PLEASE SEE ATTACHED POWERPOINT FILE

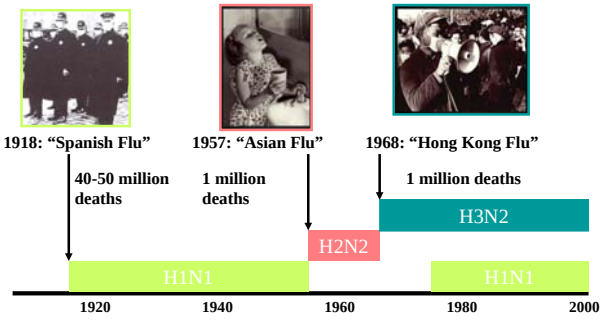
Annex I

ECDC – Nowcasting and Forecasting

Dr Peter G Grove

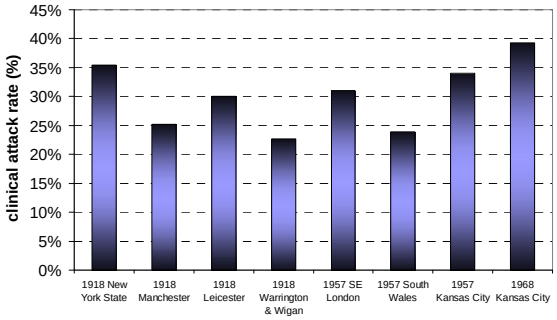
Health Protection, International Health and Scientific Development Analytical Team
Department of Health (England)
United Kingdom

Circulating influenza strains in humans and pandemics in 20th Century

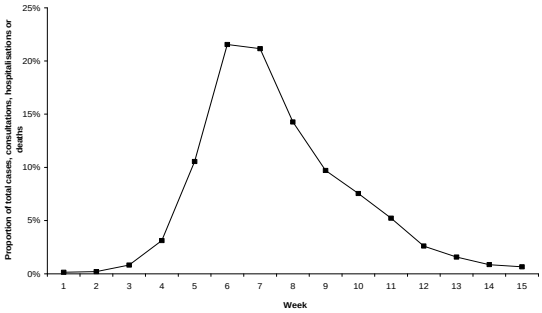


Nick Phin - HPA

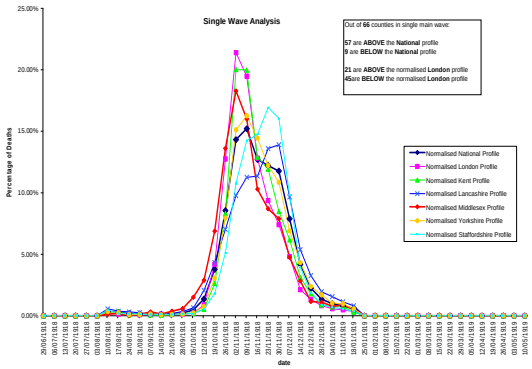
Overall clinical attack rate in previous pandemics - HPA



Single wave profile showing proportion of new clinical cases, consultations, hospitalisations or deaths by week.



1918 Regional Epidemics – 2nd Wave



Case Fatality Rate

Year	Deaths	Mortality rate	CFR
1918/19	200,000	0.50%	2.00%
1957	30,000	0.06%	0.20%
1968/69	80,000	0.15%	0.40%

Advised Planning Assumptions

- Up to 50% of the population ill (with serological rates up to 80-85%).
- Of which, from 10% up to 25% are expected to have complications, half of these bateriological. (With possibly as little a 35% overlap between the 'at risk groups' and those who actually get complications.)
- Peak illness rates of 10 - 12% (in new cases per week - of the population) in the peak fortnight.
- Absences rates for illness reach 15-20% in the peak weeks (at a 50% overall attack rate, assuming an average 7 working day absence for those without complications, 10 for those with, and some allowance for those at home caring for children.)
- Case hospitalisation demand rates in the range 0.55% to 4% with an average six day length of stay.
- - but, of which 25% would, if the capacity existed, require intensive care for 10 days.
- Case fatality rates in the range 0.4% to 2.5%.

NHS capacity and possible peak week pandemic flu demand

	New clinical cases			Acute hospital beds (critical care beds in brackets)[1]				GP			
Population	New clinical cases in peak week of up to			Normal availability [2] (acute, general and non neo-natal critical care beds, including day beds)	Expected ADDITIONAL demand for beds in peak week of up to			Normal weekly consul-tations	Expected ADDITIONAL demand in peak week of up to (assuming GPs responsible for handing out antivirals ie see all cases)		
	50% attack rate	35% attack rate	25% attack rate		50% attack rate	35% attack rate	25% attack rate		50% attack rate	35% attack rate	25% attack rate
England	5,398,400	3,778,900	2,699,200	133,200 (3,200)	198,100 (64,300)	138,670 (45,000)	99,100 (32,200)	4,672,200	5,398,400	3,778,900	2,699,200
UK	6,465,900	4,526,100	3,233,000	159,600 (3,900)	237,274 (77,000)	166,092 (53,900)	118,600 (38,500)	5,596,200	6,465,900	4,526,100	3,233,000
100,000	10,800	7,500	5,400	266 (6)	395 (128)	277 (90)	198 (64)	9,300	10,777	7,500	5,400

- 22% of cases occur in the peak week
- 3.7% case hospitalisation rate, corresponding to a 2.5% case fatality rate
- 25% of hospitalisations require critical care
- Average length of stay in hospital for patients not requiring critical care of 6 days
- Average length of stay in hospital for patients requiring critical care of 10 days

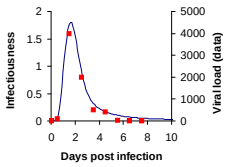
[1] Critical care beds are also included in the total number of beds
[2] It is estimated that on average about 60% of beds are occupied by emergency patients

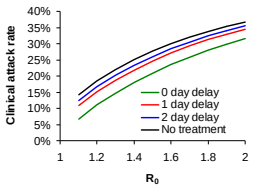
Countermeasures

- Antivirals
  - Treatment courses for 25% growing to 50% of the population.
- Antibiotics
  - Building up to treatment of all those with bacterial complications and prophylaxis of 'at risk groups'.

Need for rapid treatment - Neil Ferguson

- Infectiousness peaks soon after symptoms start for human flu.
- Hence early treatment can reduce transmission substantially (as well as having best clinical effect).
- 48h delay to treat reduces impact of treatment on transmission substantially (as well as clinical benefit).





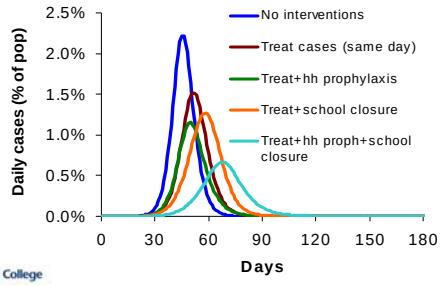
Imperial College London

Telephone System

- Triage.
- Unique reference number.
- Stay at home.
- Send 'friend' to collect antiviral.
- Delivery in exceptional circumstances.
- Arrange GP visit for those with complications or aged < 3 years.

Countermeasures

‘Household Prophylaxis’



Imperial College London

MRC

Antivirals

- At 25% level
  - Treatment of all those ill until effective attack rate is forecast to exceed 25%
  - Treatment of Children and at risk groups.
- At 50% level
  - Household Prophylaxis
  - Treatment of all
  - Treatment of Children and at risk groups.

Decisions

- If/When to change antiviral strategy?
- Whom to prioritise?
- When to open/close schools?
- (Secondary Antiviral)

Severity

- Extreme Pandemic (CFR > ~ 3%)
  - Close schools
  - Cancel public events
  - Household quarantine
  - Travel restrictions
- Mild Pandemic (CFR < 0.4, AR < 10%)
  - Revert to usual GP based approach.

Secondary care

- Assistance to localities with specific problems.

Annex II

Overview of UK surveillance - data sources, limitations and reporting systems

Dr Arlene J. Reynolds
Surveillance Manager, Pandemic Flu Team, Department of Health UK

What will be covered

- Aim & primary objectives of UK surveillance programme
- What information will be collected during a pandemic
- Approach
- Data sources, their limitations & reporting systems

Aim of UK pandemic flu surveillance programme

- To define the relevant health data to be captured, analysed, interpreted and communicated during a pandemic and to ensure that appropriate arrangements are in place and to inform decision-making

  ➢Ensure that the UK is well prepared to respond effectively to a pandemic, employing a range of measures in advance of and during a pandemic to mitigate its impact.

Primary objectives

- Ensure that systems are in place in the UK to identify, capture, analyse and interpret health data as part of an overarching surveillance package.
- Report the data in an appropriate and timely manner, avoiding duplication of reporting processes and providing as far as possible "one version of the truth".
- Communicate (enable appropriate access to the data) at all levels in the UK – local, regional, devolved administration and national – to inform decision-making.

What information will be required during a pandemic?

- The characteristics and impact of the pandemic in order to inform any intervention strategies (e.g. vaccination, treatment guidelines) to slow down its spread and manage its consequences.
- Estimates of the number of cases and deaths during the pandemic for timely reporting to those managing the pandemic at local, regional and national levels including, senior officials and Ministers and to the media.
- How health and social care services are coping.
- How effectively the key interventions are being implemented.

Approach

- Where possible systems will be built on existing data collection mechanisms that are already in place

  1. To monitor the onset, magnitude and duration of seasonal influenza (primary care based collection such as RCGP, QFlu and NHS Direct)
  2. To monitoring pressure on the health service (acute trust winter pressures data collections)

- Gaps in the required data (e.g. lack of timely death data or secondary care data) will be addressed through development and implementation of new systems.
- Work to address these gaps will be taken forward in discussion and agreement with the surveillance PIG and appropriate stakeholders.

Surveillance in UK

- HPA responsible for national disease surveillance (behalf of the DH)
- HPA provides link into international disease surveillance (WHO Ref lab for Influenza)
- HPA monitors a number of different sources → complete and accurate UK picture

Data sources - Primary Care

- Sentinel GP schemes
  - Birmingham Research Unit of RCGP (E)
  - National Public Health Service for Wales
  - Health Protection Scotland
  - Communicable Disease Surveillance Centre (NI)
  - QFlu (larger population)
- GP episode incidence rate for influenza like-illness (ILI)
  - Rate per 100,000
  - Total respiratory diseases
  - Upper respiratory tract infections
  - Lower respiratory tract infections
  - Pneumonias/pneumonitis
    - Age bands
    - Daily basis/twice weekly
    - Currently used for seasonal flu activity monitoring & are shown to be good indicators of flu activity in the community

Primary Care (contd)

- NHS direct calls –Data on 10 symptoms/syndromes are received electronically from 22 call centres (daily analysis)
  - Cough, cold/flu, fever, diarrhoea, vomiting, eye problems, double vision, difficulty breathing, rash and lumps
  - Excesses in calls highlighted
    - identify an increase in symptoms indicative of the early stages of common illness (e.g. flu) or illness caused by the deliberate release of a biological or chemical agent
- Medical Officers of Schools Association (MOSA) scheme
  - Influenza activity in school age children at boarding schools (weekly reports to respiratory dept CfI)
    - Provide early warning system that flu is circulating

Primary Care flu activity - limitations

- No one source provides all info – multiple sources to give overall picture
- Proxy figures - not clinically confirmed cases
- Not necessarily representative of UK - sentinel GP schemes
- Does not differentiate between first and subsequent episodes – overestimate
- No follow-up info on treatment or complications or outcome (deaths)

Data sources - Secondary care

- NHS Winter pressures report – indication on how services are coping
- Acute Trusts (although all NHS Trusts have the capacity to provide them)
  - A & E closures
  - A & E diversions
  - 12 hour & trolley waits
  - Trusts with operational difficulties
  - Free text box –qualitative data/comments

Secondary Care - limitations

- Tends to be more qualitative rather than quantitative
- Acute trusts only so not full picture
- Equivalent data not collected by all Devolved Administrations
- Not specific to flu
- Represents severe end of spectrum only

Mortality data

- Office of National Statistics
  - Number of deaths registered in England and Wales (estimated)
  - Weekly basis
    - Total number of deaths
    - Deaths by underlying causes (all respiratory deaths
    - Total deaths: average of comparable week over the last five years

Death data - limitations

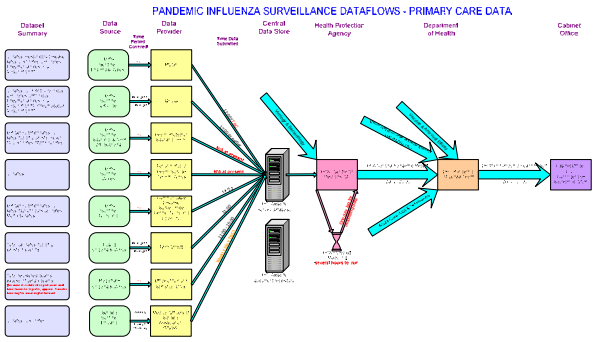
- Estimates based on numbers registered through 2 different systems
- ONS covers England & Wales only
- Separate systems in Scotland & Northern Ireland
- Not very timely – 2-3 week lag at least (likely to be more during a pandemic)
- Time period not comparable to weekly figures on number of ILI cases
- Currently no info on excess deaths
- Currently no information routinely provided on date of death & cause (key for RTM)

New or proposed data collections

- Flu line
  - No of calls, new and ongoing
  - No of people provided with antivirals
  - No of people with antivirals who have risk factors
  - No of doses of antivirals distributed (allowing stockpile control)
  - No of people referred to hospital
    - Inform anti-viral policy
    - Provides a handle of the number of flu cases
    - Provides key info for RTM (number of people affected)

New surveillance systems (cont)

- FF100 database
  - Detailed info on complications & symptoms for cases and contacts; some indication of severity of disease & outcome (unlikely to provide any info on case fatality rate due to small numbers)
    - Provide information on severity & spread of flu to inform clinical management & inform policy
- Emergency Department pilot study
  - Exploring whether detailed info on flu related info e.g. hospitalisations, complications, treatment (AV/AB given), length of stay can be extracted from A & E systems
    - provide detailed info on number of flu cases presenting at hospital and clinical picture/treatment



Annex III

From Data to Information

Resilience and Alternative Views

- Two approaches
- Three teams
  - Health Protection Agency Centre for Infections.
  - Medical Research Council Centre for Outbreak Analysis
  - Health Protection Agency Centre for Emergency Preparedness.

Data streams

- Telephone system:
  - Daily, Current, includes ILI.
  - Calls.
  - Antivirals authorised (fraud)
  - Age
  - Complications

Databases

- First 100's of cases
- Clinical database

GPs

- RCGP
- QFlu
  - Daily.
  - Complications
  - Antivirals for children under 3.
  - Hospitalisations.

- Deaths from ONS.
  - Days or weeks delay.
  - High level of background.
- Hopitalisations from standard NHS statistics.

- Daily Nowcasts
- Weekly long term forecasts.
- HPA CfI results official view
- Results compared each day – discussed with senior officials.
- Implications explained.

NOWCAST NATIONAL SUMMARY
Note: Numbers in this section are *modelled estimates*
Both current and past *estimates may change from day to day* as more information becomes available.

National Summary (ranges indicate minimum, median, and maximum estimates)	Previous week (Until [xx-?]-xx-xx)	Last week total (From xx-xx-xx)	Cumulative total since (date)
Nowcast estimate of total number of ***clinical cases***	range	range	range
Nowcast indicative estimate of total number of ***excess deaths in UK*** (based on international experience)	range	range	range
Nowcast estimate total number of ***excess deaths in UK*** (based on UK data)	range	range	range
Nowcast estimate of ***case fatality ratio*** (based on UK data)	N/A	N/A	range
Comparison with last report submitted Free text summary			

Graph 1: *Nowcast* cumulative total of clinical[ii] **cases** of pandemic influenza broken down by age group[iii].
Graph 2: *Nowcast* cumulative total of excess **deaths** from pandemic influenza broken down by age group[iii] (if modelled data exists)

Total number of antiviral treatment courses distributed	Number	Date
Total number of people vaccinated (when available)	Number	Date
Total number of Trusts with operational difficulties	Number	Date/Time
Comparison with last report submitted Free text summary		

LATEST STATISTICAL DATA (Date of latest update indicated)
NOWCAST LOCAL SUMMARY
Local graphs

Table 1. *Nowcast* estimates of new clinical cases of pandemic influenza in the last 24 hours and cumulative cases to date (based on modelled data)

	East of England		East Midlands		London		N East		N West		S East		S West		West Midlands		York & Hum		Wales		N I		Scotland		**Total**	
	New	Cum	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	**New**	**Cum**
<1 years																										
1-4 years																										
5-14 years																										
15-44 years																										
45-64 years																										
65+ years																										
Total																										

Source: Health Protection Agency

Table 2. *Nowcast* estimates of new excess deaths due to pandemic influenza in the last 7 days and cumulative excess deaths to date

	East of England		East Midlands		London		N East		N West		S East		S West		West Midlands		York & Hum		Wales		N I		Scotland		**Total**	
	N	Cum ew	N m	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	**N**	**C um ew**
<1 years																										
1-4 years																										
5-14 years																										
15-44 years																										
45-64 years																										
65+ years																										
Total																										

Table 4. Modellers forecasts and projections – Epidemiology (if available)
Free Text

Annex IV

ECDC Nowcasting and Forecasting Workshop
November 2007

Pandemic Influenza: A beginning to epidemic forecasting

Ian Hall, Iain Barrass, *Ray Gani, Helen Hughes*, Steve Leach

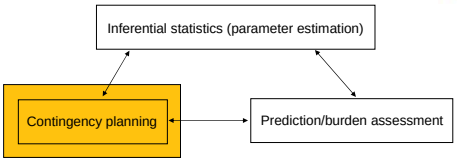
Microbial Risk Assessment
Centre for Emergency Preparedness and Response
Health Protection Agency, UK

Why do we need real time models?

- To monitor hospital capacity
- To check health care system resilience
- To monitor absenteeism levels
- To assess logistical demands – antiviral stockpile and delivery
- To provide reassurance to the public
- To provide evidence of control methods working as expected
- Adjust plans and advice as the situation develops

Somehow we must predict future incidence *and* infer key previously unknown parameters.

Real time modelling



Models will be run during response

Integrated model needed for parameter estimation and future incidence prediction

Model only as effective as surveillance systems allow

Manage expectations!

Pandemic Influenza

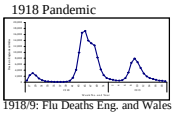
Three pandemics during 20th Century (1918, 1957, 1968)

20 million deaths worldwide in 1918-19

Different data sources

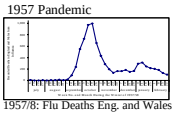
Current and real threat

1918 Pandemic



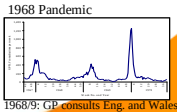
1918/9: Flu Deaths Eng. and Wales

1957 Pandemic



1957/8: Flu Deaths Eng. and Wales

1968 Pandemic



1968/9: GP consults Eng. and Wales

Exemplar data sources

Any data source will miss cases – e.g.
- Asymptomatic cases
- Only a proportion of symptomatic cases will report to primary care, etc.

Data sources will have different delays in reporting
- Mortality needs to be registered
- Other Data need to be entered, checked, etc.

Excess Mortality (ONS)

GP consultations (RCGP, Qflu, …)

Hospital Episode Statistics (Pneumonia etc)

National Insurance claims (proxy for absenteeism in 1957)

First few hundred surveillance database

Exponential growth fitting

Linearise SEIR model

↓

Derive eigenvalue

However, this does not tell us about:

The final size of the outbreak,

The expected peak week,

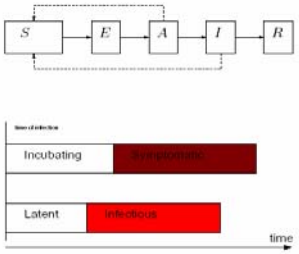
In practice it is difficult to reliably measure the growth rate *(high spatial aggregation/coarse reporting timescale/noise in data).*

Can we predict Pandemic influenza incidence from data?

Hall et al, E&I, 2006.

Let us assume actual UK influenza incidence will follow a 'classical' epidemic curve

$$\frac{dS}{dt} = -\frac{\tau_R R_E}{\tau_I+\tau_A}(I+A)S,$$
$$\frac{dE}{dt} = \frac{\tau_R R_E}{\tau_I+\tau_A}(I+A)S - \tau_R\tau_E^{-1}E,$$
$$\frac{dA}{dt} = \tau_R\tau_E^{-1}E - \tau_R\tau_A^{-1}A,$$
$$\frac{dI}{dt} = \tau_R\tau_A^{-1}A - \tau_R\tau_I^{-1}I,$$
$$\frac{dR}{dt} = \tau_R\tau_I^{-1}I,$$



We must then convert the model output to match the observed data – e.g. for *new symptomatic* cases → $I_w^R = S_f N\left[I\left(t+\frac{\tau_S}{\tau_R}\right)+R\left(t+\frac{\tau_S}{\tau_R}\right)\right]_w^{w+1}$,

We have 10 parameters in total in this model:

- The frequency of reporting
- The number in the population
- The latent period
- The symptomatic period
- The infectious period
- Immunity level in population
- Size of importations
- Date of importations
- The effective reproduction number
- The proportion of cases reflected by the data in question

We have 10 parameters in total in this model:

- The frequency of reporting
- The number in the population

Data dependent - known

- The latent period
- The symptomatic period

Epidemiological studies home and abroad

- The infectious period

Parameter estimation methods

- Immunity level in population
- Size of importation(s)

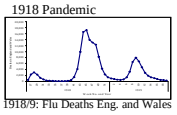
Assumed small

- Date of importation(s)
- The effective reproduction number
- The proportion of cases reflected by the data in question

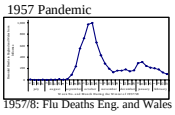
Unknown *but* reasonably bounded

Parameter estimation methods

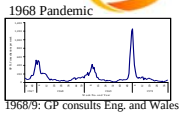
Pandemic Influenza


1918 Pandemic

1918/9: Flu Deaths Eng. and Wales


1957 Pandemic

1957/8: Flu Deaths Eng. and Wales


1968 Pandemic

1968/9: GP consults Eng. and Wales

Assuming

- 2 day latent, 1 day asymptomatic infectious, 1.5 day symptomatic infectious periods

---

- +/- Bounding Estimates ("Expectation" +/- 50% [rather gross estimate of uncertainty])

"Expectation"

- RCGP (1 in 5 symptomatic cases report to GP & 50% cases are asymptomatic) – scaling factor 0.1

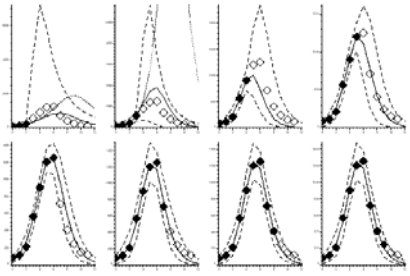
Parameters adjusted are:

$$\Delta = \sum_{w=0}^{M-1} r_w^2 = \sum_{w=0}^{M-1} [I_w - \gamma I_w^R(\tau_S, R_E)]^2,$$

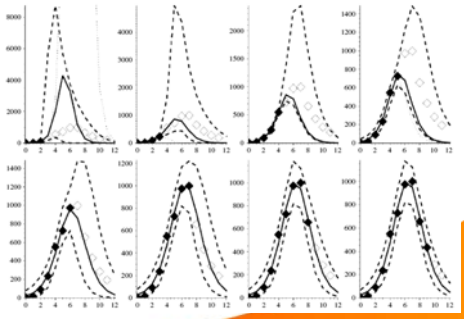
1. The effective reproduction number
2. A temporal shift constant
3. The ratio of recorded incidence to infectious cases (scaling factor)

Result of procedure using data from 1969 main pandemic wave

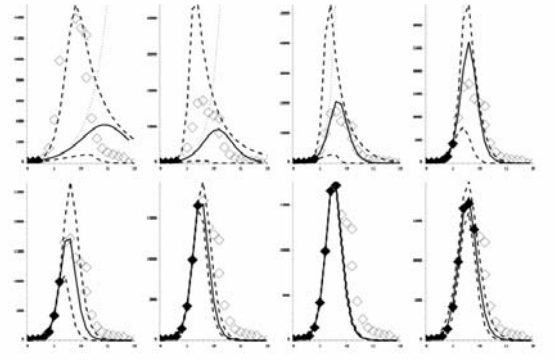
- Reasonable fit before the peak (4/5 weeks)
- Sound fits around peak and after
- MLE poor if scaling factor is unbounded
- Future incidence within 95% credible intervals



Result of procedure using data from 1957 pandemic wave

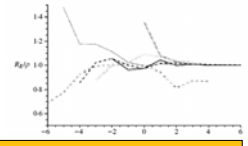


Result of procedure using data from 1918 main pandemic wave



Summary results from historical UK data sources

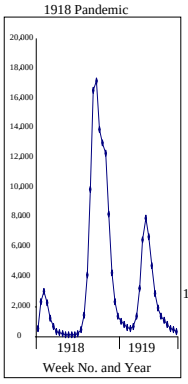
Year	Wave	ρ	Γ	X^+	X^-
1918	1	1·83	0·0004	0·0006	0·0002
1918	2	1·73	0·0027	0·00405	0·00135
1918	3	1·54	0·0017	0·00255	0·00085
1957	1	1·50	0·0002	0·0003	0·0001
1968	1	1·28	0·08	0·12	0·04
1968	2	1·56	0·09	0·135	0·045



Measure of fit	Weeks used in estimate	1918 wave 1 (peak in week 3)	1918 wave 2 (peak in week 9)	1918 wave 3 (peak in week 6)	1957 (peak in week 8)	1968 wave 1 (peak in week 5)	1968 wave 2 (peak in week 7)
Relative error in amplitude of predicted and observed epidemic peaks	4	1·04	0·54	1·29	0·87	0·98	1·51
	5	1·02	1·19	1·41	0·86	1·06	0·80
Difference in timing of observed and predicted epidemic peak (weeks)	4	0	3	1	−2	1	0
	5	0	0	1	−2	1	−1
Difference in epidemic 'duration'	4	−1	−1	−1	−4	2	0
	5	−1	−4	−1	−4	2	−2

Compared to "guessing" based on past experience?

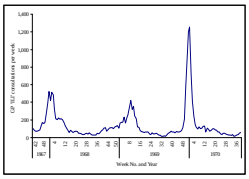
1918 Pandemic



1918/9: Flu Deaths Eng. and Wales

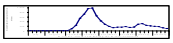
Different pandemics had very different dynamics and impacts (both between waves of the same pandemic and between different pandemics)

1968 Pandemic



1968/9: GP consults Eng. and Wales

1957 Pandemic "scaled" to match 1918



1957/8: Flu Deaths Eng. and Wales

Possible extensions/improvements

Delays – (include reporting "model")

Improved Spatial and temporal resolution to observations

Consider Hetero & Homo -typic imunity?

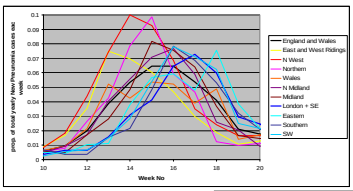
Bayesian inference methods / MCMC techniques

Incorporate heterogeneities – i.e. age structure

Fitting to multiple data stream simultaneously

Predict spatial trends nationally?

1957 data showing spatial separation of local epidemics

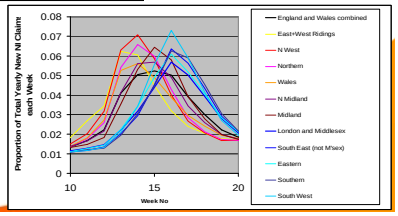


Clear spatial grouping of regions in both datasets

Pneumonia cases

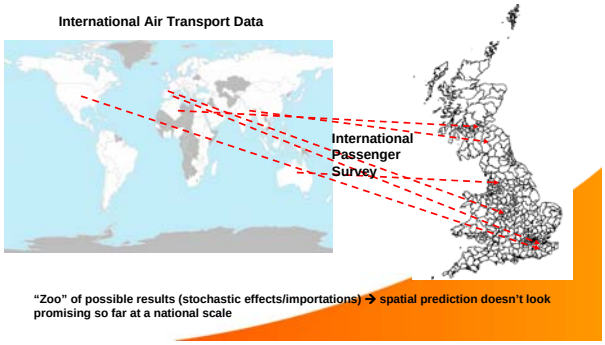
1957 Asian flu pandemic main wave

NI claims



Approach - Simulation

(International Spread →National Importation + Spread)



Annex V

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Statistics for the real-time monitoring of a pandemic

Simon Cauchemez

Dept. of Infectious Disease Epidemiology
Faculty of Medicine
Imperial College

Imperial College London

I- Estimation of key clinical & epidemiological indicators

- Key clinical indicators:
  - Case fatality ratio, incubation period, duration of symptoms…
  - Estimation based on detailed epidemiological investigation of the first few hundred cases in the UK + epidemiological data from other countries.
- Basic epidemiological indicators:
  - Number of cases, number of deaths…
  - Estimation based on various surveillance sources (telephone triage system, Qflu, Sentinel hospital data, cohort survey).
- Statistical issues: under-reporting, sampling bias, reporting delays, imputation from multiple sources…
- Critical to correct for those biases to avoid misleading analysis…

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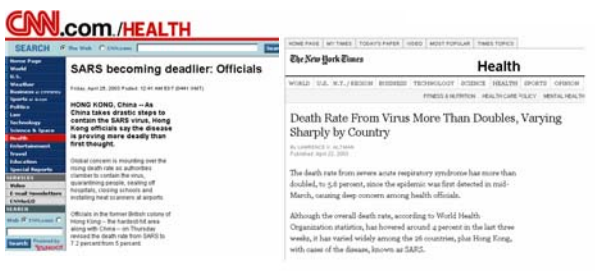
… and panic!

Case fatality ratio: proportion of cases who eventually die from the disease.

Crude estimates can be very misleading if, at the time of the analysis, the outcome (e.g. death or recovery) is unknown for an important proportion of patients.



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Proportion of observations censored in the SARS outbreak

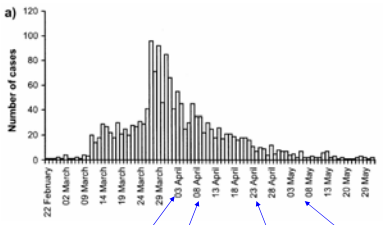
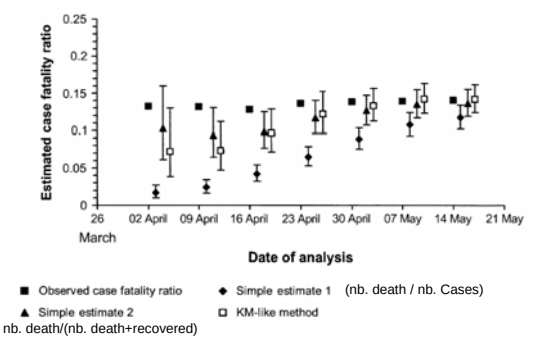


TABLE 1. Summary of the number of cases and the degree of censoring at different time points for the epidemic of severe acute respiratory syndrome in Hong Kong, 2003

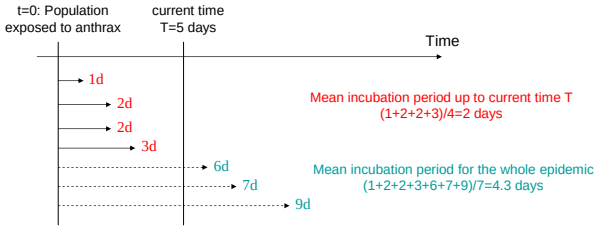
	Date						
	April 2	April 9	April 16	April 23	April 30	May 7	May 14
No. of cases	925	1,201	1,367	1,489	1,547	1,582	1,607
% of observations censored	85.9	81.2	71.5	51.6	35.1	25.2	17.3

[Ghani et al, AJE, 2005]

Statistical methods to correct for censorship
[Ghani et al, AJE, 2005]



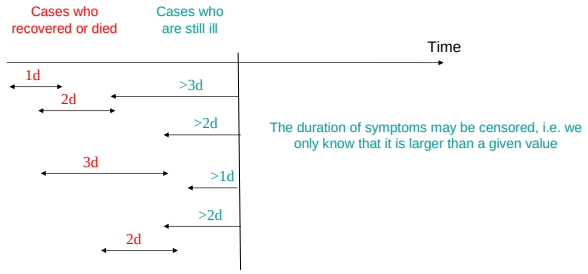
Truncated incubation period
[Brookmeyer, Biostatistics, 2001]



- We first observe cases with short incubation period;
- When we naively estimate the incubation period in real-time, we under-estimate it!

Truncated data: we only observe incubation periods which are ≤5 days.

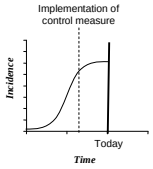
Censored durations of symptoms



Censored data are very common in biostatistics – survival analysis.

II- Are we winning the battle?

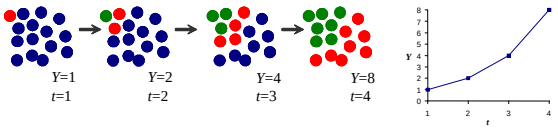
Simple and robust methods to evaluate the efficacy of control measures



Are control measures efficacious? Do we need to reinforce them?

Reproduction number R

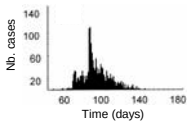
- Epidemics spread through contact (e.g. person to person):



- *Reproduction number R_t*: number of secondary infections caused by one case at time t.
- Epidemic "under control" for $R_t<1$.
- Monitoring R_t is a natural way to evaluate whether the epidemic is under control.

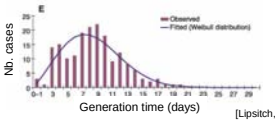
Inferring Who-Infected-Whom
[Wallinga and Teunis, AJE, 2004]

- Data (SARS):
  - Epidemic curve:



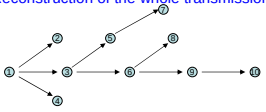
  - Generation time:

Time between symptoms onset of *infector* and symptoms onset of *infectee*;



[Lipsitch, Science,2003]

- Output: Reconstruction of the whole transmission tree (who-infected-whom)



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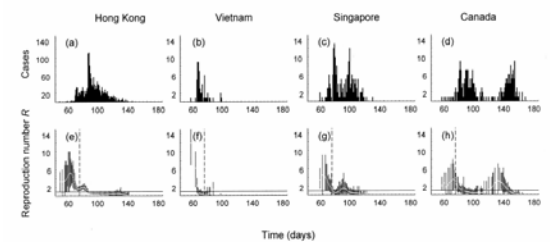
Retrospective analysis of the SARS outbreak

[Wallinga and Teunis, AJE, 2004]



SARS 2003

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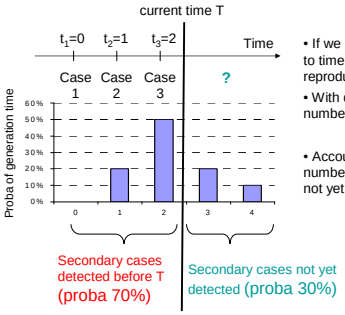
Underestimation of R in real-time

[Cauchemez et al., EID 2006]



- If we naively estimate R_1 from data available up to time T, on average, we underestimate the reproduction number by 30%.
- With data available up to time T, the expected number of secondary cases detected before T is:

$E(R_1^-)=1.71$

- Accounting for censorship, the corrected number of secondary cases (detected before T + not yet detected) is:

$E(R_1)=1.71/0.7=2.44$

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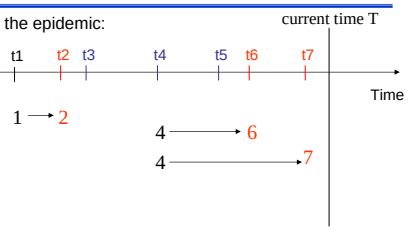
Uncertainty on the generation time

[Cauchemez et al., AJE 2006]

- Data collected during the epidemic:
  - Symptom onset:
  - Case tracing:



- Generation time:
  - At first, the generation time is unknown;
  - First estimates of the mean and variance of GT have a large variance;
  - During the course of the epidemic, estimates become more precise.

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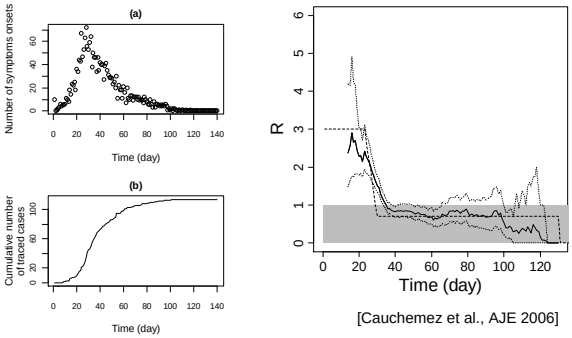
Monitoring the efficacy of control measures in real-time

- SARS-like outbreak: 5% of the cases are traced; 2086 cases;114 traced cases.



[Cauchemez et al., AJE 2006]

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III- Estimating transmission parameters of the pandemic strain

Plans are written before the pandemic, under a set of assumptions on the future pandemic strain.

Can we validate assumptions made for planning? And update models if necessary

Epidemiological question	Consequences for control
• What is the efficacy of antiviral drugs to reduce susceptibility of prophylaxed ind., infectivity of cases?	• Benefit of treatment? Prophylaxis?
• What is the relative susceptibility-infectivity of children?	• Should we specifically target children? School closure?
• What is the importance of household transmission?	• Should we target households? Prophylaxis of household members?

--We may not have answers at the time when decisions have to be made--

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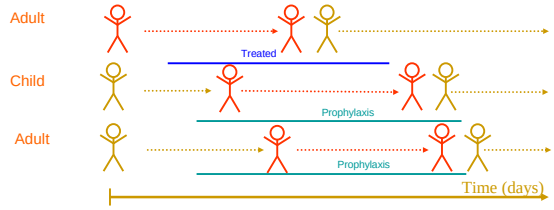
Estimation based on follow-up of households

- Study design: if a case is detected, follow-up of symptoms in his/her household for the next XX days [e.g. Carrat et al., Arch Intern Med, 2002]:



- Inference is challenging because:
  i) *Incomplete observation*: we don't know when, where and by whom a case was infected;
  ii) *Competitive risks of infection*: infection from the community or from any infective member.

- But sophisticated statistical methods exist to cope with those issues: e.g. Markov chain Monte Carlo & data augmentation techniques [Cauchemez et al., Stat Med, 2004]

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Summary

- A pre-requisite for "real-time modelling" is to have access to good surveillance data in real-time!
- Monitoring the pandemic will be very challenging! Even the simplest questions (e.g. what was the number of cases yesterday in the UK?) are far from simple!
- Statistical issues: reporting delays, sampling bias, under-reporting, imputation from multiple sources…
- We may not be able to answer all the questions at the time when decisions have to be taken! (e.g. efficacy of antiviral drugs to mitigate the pandemic).

Annex VI

Winter Willow

Surveillance and Real Time Modelling

- Winter Willow did not exercise real time modelling or surveillance systems directly
- But…

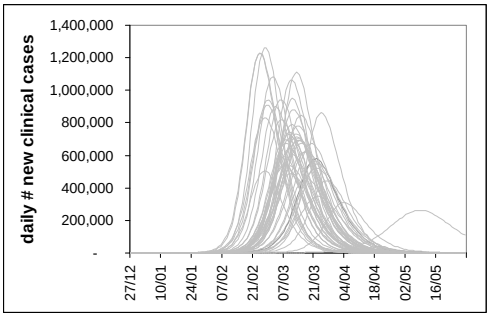
- Large number of simulated data sets, forecasts and reports had to be created.

Simulated data

- Run model to construct epidemic (cases by age, hospitalisations, deaths.)
- Add noise (ILI, delays in reporting)
- Create simulated data set.
- Run nowcasts and forecasts.
- Use reporting system to present to decision makers.

- Lessons to be learnt from process of creating reports and how they were used.

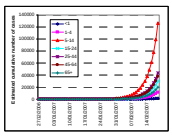
Forecasts at first case.....



UK Alert level : 4 declared on: 19th February 2006 Report Date: 19th February 2006

Summary	This week so far	Last week total	Cumulative total
Estimated Total number of clinical cases[2] (modelled data)	220,000	41,000	270,000
Estimated Total number of excess deaths (modelled data)	TBC	TBC	TBC
Indicative cumulative number of deaths (modelled)	N/A	N/A	1272
Total number of antiviral treatment courses distributed	N/A	N/A	341,928
Total number of people vaccinated (when available)	N/A	N/A	NONE
Total number of Trusts with operational difficulties	N/A	N/A	N/A
Comparison with last report submitted Free text summary: The number of clinical cases is increasingly exponentially in all regions now. The incidence in school-aged children continues to be significantly higher than in other age groups. There continues to be a large discrepancy between the estimated number of cases and the number of antiviral doses given (though the difference is falling). This highlights that many individuals have received antivirals for ILI that was not pandemic influenza in the early phases, but as the incidence increases, the "wastage" rate is now dropping significantly. Although there are many case reports of deaths, the number of deaths reported by ONS is still not above the base-line due to delays between illness onset and death, registration and in reporting of deaths.			

Graph 1: Cumulative total of clinical[2] **cases** of pandemic influenza broken down by age group[3]



Graph 2: Cumulative total of excess **deaths** from pandemic influenza broken down by age group[3]

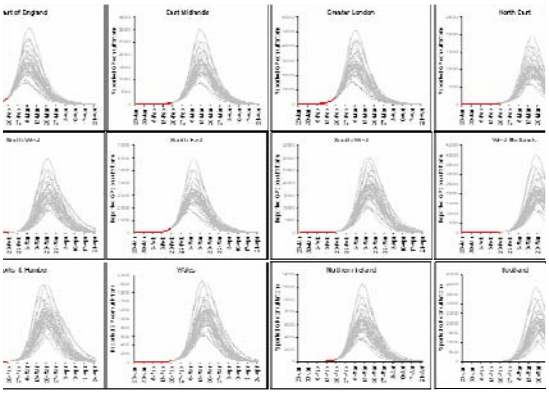
Page 1 of 7

Table 3. HPA commentary
There is considerable uncertainty in projections at present, since the number of reported consultations has only just risen above base-line levels in most regions. In particular, due to the delay between onset and reporting, projections on deaths is speculative, and informed from estimates made from non-UK specific data. Detailed projections on deaths by age and region are therefore not reliable at this time and are therefore not shown.

Table 4. Modellers forecasts and projections – Epidemiology (if available)
Short-term forecasts (next 5 days): 622,000 new cases are projected to occur in the next 5 days, roughly half of which are expected in children under 15 years age. The table below gives the breakdown of expected cases by region (to nearest 000):

East of England	East Midlands	Greater London	North East	North West	South East	South West	West Midlands	Yorks & Humber	Wales	Northern Ireland	Scotland
142,000	26,000	215,000	9,000	10,000	151,000	16,000	10,000	10,000	9,000	15,000	9,000

Long-term projections (last updated 19/2/07):
The figure compares GP consultation data (red) with model projections (grey). The expected number of cases over the course of the epidemic is 16.1m, with 90% CI from (8-25m). The expected number of excess deaths is 374,000 (90%CI 192,000-593,000). London and the South East are expected to peak in early March, Yorks & Humber, Scotland and North West late March. Other regions are expected to peak around mid-March.



- *Surveillance and Real-time modelling are critical to management of a pandemic*

Databases

- First 100's of cases
- Clinical database

Lessons

- Senior Policy Makers did not understand what the numbers meant.
- Understanding was corrupted by 'Chinese whispers'

Lessons

- Need better *process*.
- Need better *presentation*.

Presentation

- Need to revisit reports
- Ranges/Dates
- Clarity of descriptions (Modelled/Actual)
- Structure

Concept

- To separate modelled 'nowcast' results from statistical data.
- To put a clear 'health warning' on the modelled data with a 'nowcast' branding.
- To present all modelled data as ranges.
- To put dates on all statistical data.

Process

- Need 'Weather Forecast' briefing by experts – at all meetings
- Data must be presented by those who understand it
- Capacity at HPA

Annex VII

Currently available epidemiological and virological surveillance data: European Influenza Surveillance Scheme - 1996-2007

John Paget, EISS Co-ordination Centre, NIVEL

Presentation

1. Background
2. Available data
3. Examples
4. Access to the data

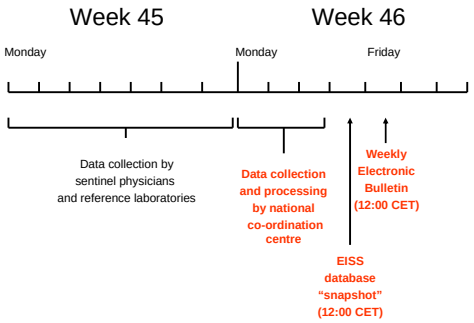
Background

- 7 countries in 1996; now 35 countries
- Web-based (www.eiss.org)
- European Commission Designated Surveillance Network (e.g. EuroTB, EuroHIV)
- Has operated from NIVEL, Utrecht, the Netherlands since November 1999
- Will be operated from ECDC as of 2 September 2008

Background

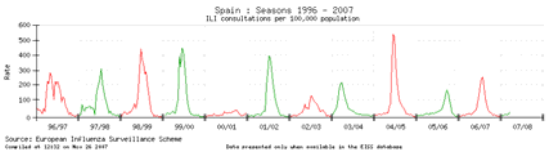
- **Total area (light green) = 4.3 million km²**
- **Total population = 498 million**
- **25,750 sentinel physicians / providers**

Weekly Electronic Bulletin



Epidemiological data

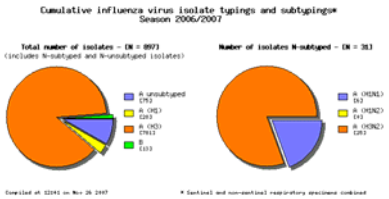
- ILI/ARI rates by week and age group
- Geographical spread indicator by week
- Intensity indicator by week



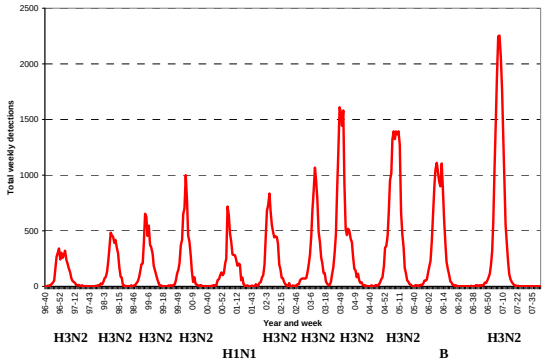
Virological data

- Total positive specimens by week and source
- Total tested specimens by week and source
- Dominant type by week
- Basic characterisation data by week (since 2000)

England:



Total Influenza ~~and RSV~~ detections per week: Europe, 11 seasons (1996-2007)

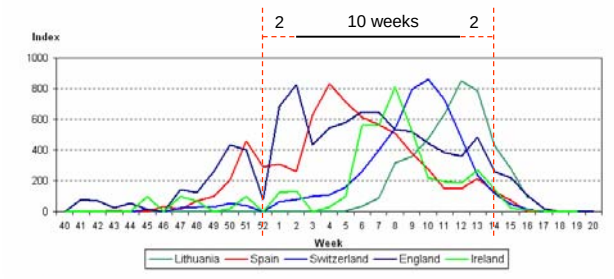


Epidemiological and Virological data: 1996-

		1996-97	1997-98	1998-99	1999-00	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08
1	BELGIUM												
2	ENGLAND												
3	FRANCE												
4	GERMANY												
5	NETHERLANDS												
6	SCOTLAND												
7	SPIAN												
8	WALES												
9	PORTUGAL												
10	CZECH REPUBLIC												
11	SWITZERLAND												
12	ITALY												
13	IREALND												
14	SLOVENIA												
15	SWEDEN									Vir			
16	DENMARK												
17	POLAND												
18	ROMANIA												
19	SLOVAKIA												
20	LITHUANIA												
21	N. IRELAND												
22	NORWAY												
23	LUXEMBOURG												
24	LATVIA												
25	AUSTRIA												
26	MALTA												
27	ESTONIA												
28	GREECE												
29	HUNGARY												
30	CYPRUS										Epi	Epi	Epi
31	SERBIA												
32	BULGARIA												
33	FINLAND									Vir	Vir	Vir	
34	UKRAINE												
35	CROATIA											Vir	Vir
	SEASONS	12	11	10	9	8	7	6	5	4	3	2	1

= Both Epi and Vir

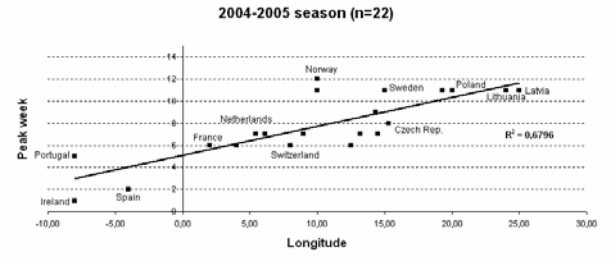
Epidemiological data: season length

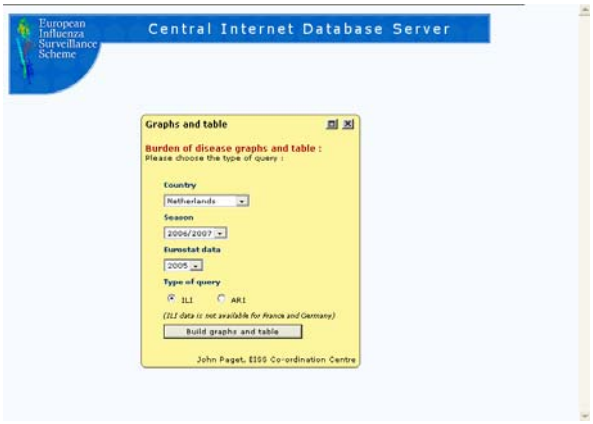


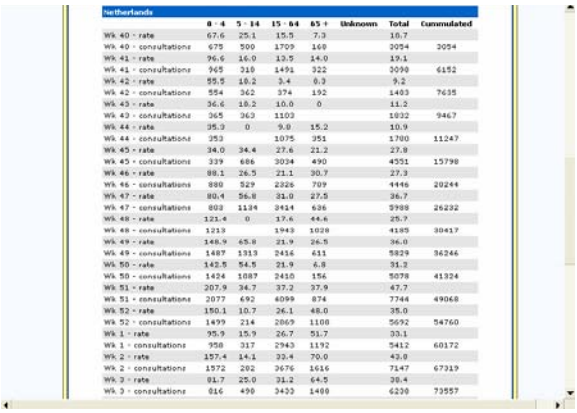
Conservative season length (Europe) = 14 weeks

Result: season length

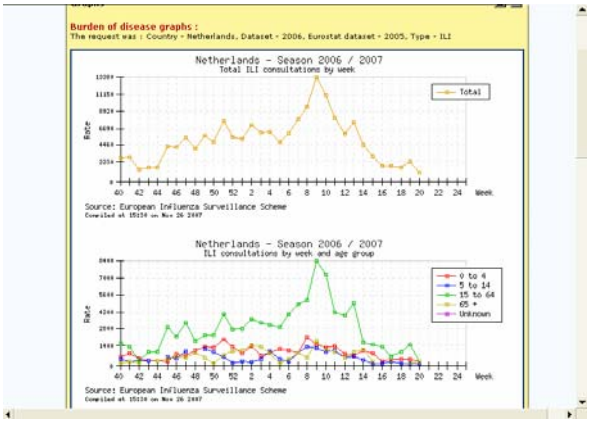
Season	Countries	Length (wks)
2006-07	28	14
2005-06	17	14
2004-05	22	18
2003-04	23	19
2002-03	17	15
2001-02	17	15
2000-01	16	18
1999-00	14	12
Average		**15.5 ~ 4 mths**





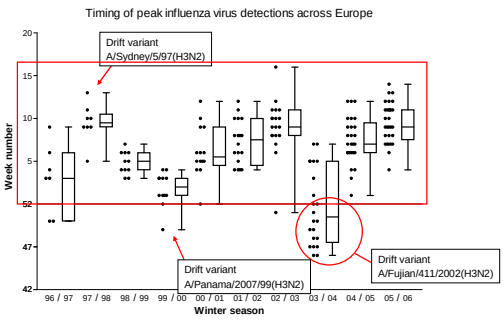


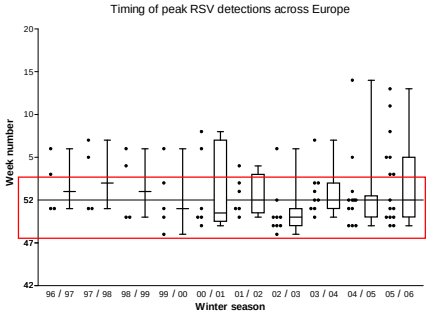
Netherlands	0 - 4	5 - 14	15 - 64	65 +	Unknown	Total	Cummulated
Wk 40 - rate	67.6	25.1	15.5	7.3		18.7	
Wk 40 - consultations	675	500	1709	169		3054	3054
Wk 41 - rate	96.6	16.0	13.5	14.0		19.1	
Wk 41 - consultations	965	318	1491	322		3096	6152
Wk 42 - rate	55.5	16.2	3.4	0.3		9.2	
Wk 42 - consultations	554	362	374	192		1483	7635
Wk 43 - rate	36.6	16.2	10.0	0		11.2	
Wk 43 - consultations	365	363	1103			1832	9467
Wk 44 - rate	35.3	0	9.0	15.2		10.9	
Wk 44 - consultations	353		1075	351		1780	11247
Wk 45 - rate	34.0	34.4	27.6	21.2		27.9	
Wk 45 - consultations	339	686	3034	490		4551	15798
Wk 46 - rate	88.1	26.5	21.1	30.7		27.3	
Wk 46 - consultations	880	529	2326	709		4446	20244
Wk 47 - rate	80.4	56.8	31.0	27.5		36.7	
Wk 47 - consultations	803	1134	3414	636		5988	26232
Wk 48 - rate	121.4	0	17.6	44.6		25.7	
Wk 48 - consultations	1213		1943	1028		4185	30417
Wk 49 - rate	148.9	65.8	21.9	26.5		36.0	
Wk 49 - consultations	1487	1313	2416	611		5829	36246
Wk 50 - rate	142.5	54.5	21.9	6.8		31.2	
Wk 50 - consultations	1424	1087	2410	156		5078	41324
Wk 51 - rate	207.9	34.7	37.2	37.9		47.7	
Wk 51 - consultations	2077	692	4099	874		7744	49068
Wk 52 - rate	150.1	10.7	26.1	48.0		35.0	
Wk 52 - consultations	1499	214	2869	1108		5692	54760
Wk 1 - rate	95.9	15.9	26.7	51.7		33.1	
Wk 1 - consultations	958	317	2943	1192		5412	60172
Wk 2 - rate	157.4	14.1	33.4	70.0		43.8	
Wk 2 - consultations	1572	282	3676	1616		7147	67319
Wk 3 - rate	91.7	25.0	31.2	64.5		38.4	
Wk 3 - consultations	916	498	3433	1488		6238	73557



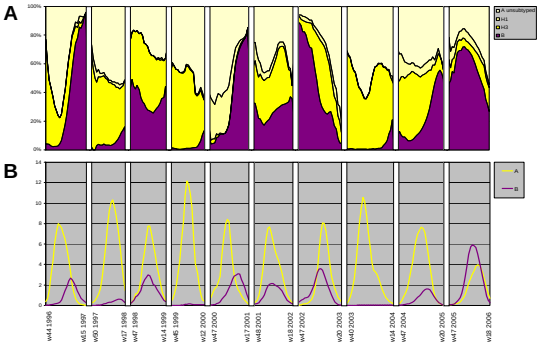
Total consultations 2006-2007: 171,952

Virological data





Ten years of European influenza virological data collected by EISS

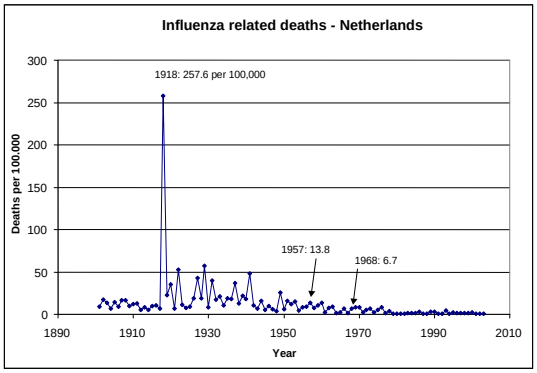


A Weekly relative distribution of influenza virus detections (100% stacked area, 5 weeks moving average)
B Weekly detections of influenza viruses (percentage of total detections in a season, 5 weeks moving average)

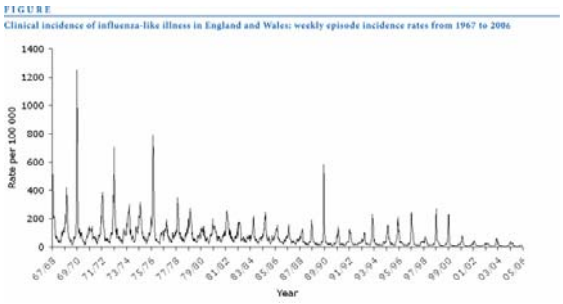
Access to the EISS data

See:
EISS Principles of Collaboration (May 2007)

Thank you for your attention

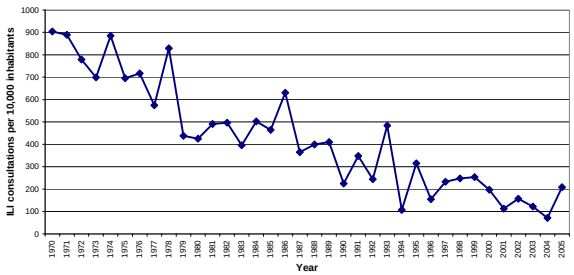


Mortality data, Central Bureau of Statistics



- Peak: 1250 per 100,000 (69/70) versus about 50 per 100,000 (05/06) – factor of 25
-The system has been since been computerised → more robust

Annual ILI consultation rates, the Netherlands, 1970-2005



Annex VIII

Real-time modelling and estimation of time-varying variables

Jacco Wallinga

Why real-time modelling & estimation of time-varying variables ?

- Making decisions in the face of uncertainty
- Epidemiological characteristics of a new, emerging infection are unknown
  - Such as SARS was in 2003
- Epidemiological characteristics of a known infections differ between pandemics, and between waves
  - Such as pandemic influenza AH1N1 in 1918 and H2N2 in 1957

The advantage of using a model

- Quantitative predictions of incidence
- Estimation of epidemiological key variables
- Optimise control policies

- Alternative: expert opinions
  - likely to miss non-linear, counter-intuitive results

The dark side of modelling: indeterminacy

- Observations do not uniquely determine the single best model structure and best set of parameter values
  - structured host population with *n* groups:
    - *n* x *n* parameters to be estimated from *n* data points

The advantage of using two models

- Similar results from 2 different models give more confidence to the results
- Different results are informative

The advantage of using ensembles of models

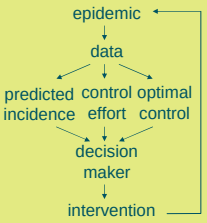
- Ensembles of causal transmission models allow for robust results
- Calculate averages over ensembles
  - weighted by likelihood of the model, given the data
- Find outcomes that hold for ensembles
  - find criteria for which the outcome must hold

- References

  - Wallinga J, Lipsitsch M. real-time estimation of impact of targeted intervention strategies during an epidemic. In preparation (2007).
  - Wallinga J, Lipsitsch M. How generation intervals shape the relation between growth rates and reproductive numbers. Proceedings of the Royal Society, Series B 274: 599-604 (2007).
  - Wallinga J, Teunis P, Kretzschmar M. Using social contact data to estimate age-specific transmission parameters for infectious respiratory spread agents. American Journal of Epidemiology 164: 936-944 (2006).
  - Heisterkamp S.H., A.M.L. Dekkers, J.C.M. Heijne. Automated detection of disease outbreaks: hierarchical time series models, Statistics in Medicine 2006, 25, 4179-4196
  - Wallinga J, Teunis P. Different epidemic curves for Severe Acute Respiratory Syndrome reveal similar impacts of control measures. American Journal of Epidemiology 160: 509-516 (2004).

What data are required for model ensembles?

- Depends on the objective
  - quantitative predictions of incidence
  - estimation of epidemiological key variables
  - optimise control policies



Quantitative predictions of incidence

- Data requirement:
  - time of symptom onset

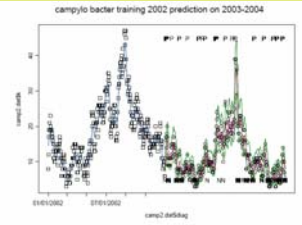
Quantitative predictions of incidence

- Heisterkamp S.H., Dekkers A.M.L., Heijne J.C.M. Automated detection of disease outbreaks: hierarchical time series models, Statistics in Medicine 2006, 25, 4179-4196

- Bayesian time series approach
- Hierarchical Model
  - random effect on each time point
  - expectation conditionally dependent on past
  - fixed effects represented by confounding variables
- Empirical Bayesian estimation
  - algorithm for penalised likelihood using standard GLM-software

Quantitative predictions of incidence

- Accurate prediction of campylobacter positive test results from Dutch laboratories
- No causal transmission model postulated in this algorithm



Estimation of epidemiological key variables

- Data requirement:
  - time of symptom onset
  - for some cases: id of source case

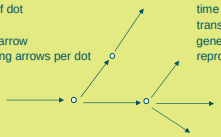
Epidemiological key variables

- Reproductive number *R* is defined as the number of secondary cases per primary case
- The generation interval τ is the duration between onset of symptoms of a secondary case and its primary case

Estimation of epidemiological key variables

- Wallinga J, Teunis P. Different epidemic curves for Severe Acute Respiratory Syndrome reveal similar impacts of control measures. American Journal of Epidemiology 160: 509-516 (2004).

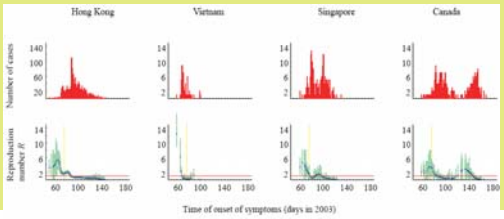
- Infection trees
  - dot — case
  - position of dot — time of symptom onset
  - arrow — transmission of infection
  - length of arrow — generation interval
  - nr. outgoing arrows per dot — reproduction number



- Apply model averaging tricks to all plausible infection trees, given the observed epidemic curve

Estimation of epidemiological key variables

- Tracking of reproduction numbers *R* of SARS outbreaks
  - *R* in uncontrolled situation is around 3
  - *R* in controlled situation is around 0.7
- Infection trees act as causal transmission models



Optimise control policies

- Data requirement:
  - group-specific risk of infection
  - only if there are substantial differences among groups:
    - group-specific infectivity, proneness-to-infection, immunological naïveté, efficacy of intervention

Optimise control policies

- Wallinga J, Lipsitsch M. real-time estimation of impact of targeted intervention strategies during an epidemic. In preparation (2007).
- Wallinga J, Teunis P, Kretzschmar M. Using social contact data to estimate age-specific transmission parameters for infectious respiratory spread agents. American Journal of Epidemiology 164: 936-944 (2006).

- Identify the best allocation of limited intervention measures (social distancing, vaccination) over groups
  - objective is to minimise future spread (*R*)

Optimise control policies

- Is it possible to observe group-specific risk of infection?
- Reconstruct age-specific, weekly numbers of susceptibles and new infections during the 1957-1958 influenza A H2N2 pandemic in the Netherlands
  - number of influenza-related deaths June 1957-June 1958
  - serological data collected in June 1957 and June 1958

Optimise control policies

- It is possible to identify the best allocation of intervention measures to minimise *R*
  - without knowing the values of the transmission parameters
  - without knowing the reproductive number
  - assuming the disease is contagious
  - assuming at-risk contacts are reciprocal

Data requirements

- Data that has to be collected during an epidemic
  - Linelist
    - case ID
    - date of symptom onset
    - ID of most likely infector
    - group membership (age, sex, occupation)
  - Population at risk
    - size of groups in population
    - number of susceptibles in population
  - Only if there are substantial differences among groups:
    - group-specific infectivity, proneness-to-infection, immunological naïveté, efficacy of intervention

Our approach to now-casting and short-term forecasting

- Doesn't exist as such
- Construct models to analyse incoming data
  - US: MIDAS
  - EU: Modelrel, Inftrans, Flumodcont
- Exploit properties of ensembles of models to obtain robust results and avoid overly specific assumptions
- Indicate what data is required to answer which question

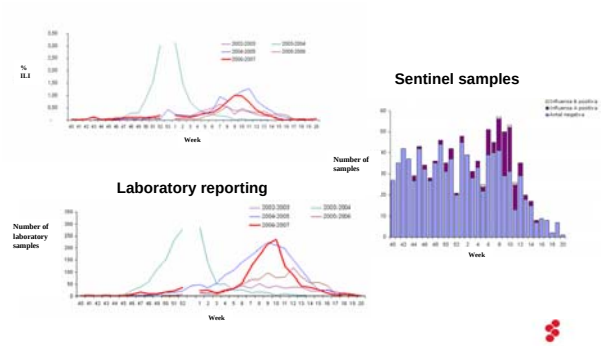
Annex IX

Population-based surveillance of influenza

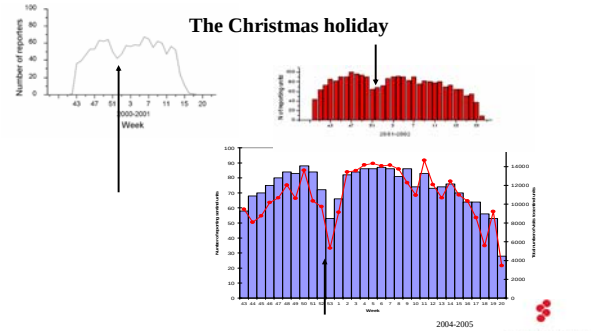
20071129

Hanna Merk
Swedish Institute for Infectious Disease Control

Sentinel reporting

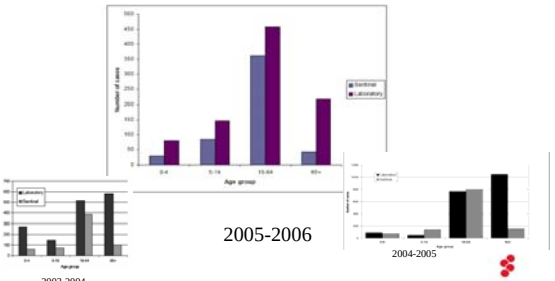


Surveillance problem



Surveillance problem

Same season but different age distribution



Surveillance problem

Sentinel: 1 % ILI (of all consultations)

Random sample: 3,6 % ILI (of all Swedish residents)

Payne et al, 2005

Actively contacting participants

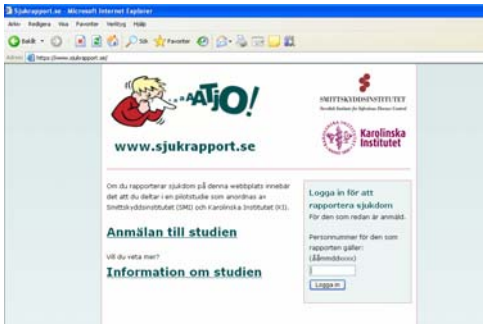
March 2006

- IVR, SMS and telephone interview.
- Calls during five consecutive week days.

- Technical problems with the IVR.
- Inadequate coverage in the telephone directory.
- Inconvenient for the participants.
- Costs.

Final Goal

- Achieve accurate surveillance of the spread of influenza in the general population.
- Achieve close to real-time surveillance.
- A complement to laboratory and sentinel surveillance.



Annex X

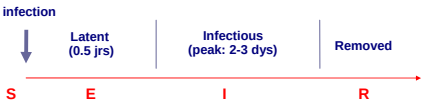
A "small-world-like" model for influenza pandemics : structure and intended use

A model developed by F CARRAT (INSERM; Paris, France) for use at Institut National de Veille Sanitaire (InVS)

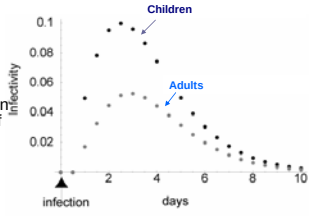
F Carrat

presented by : PY Boëlle / I Bonmarin

Natural history of infection



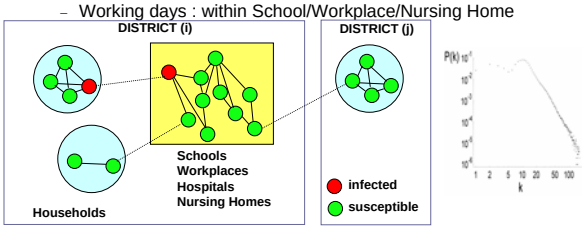
- Infectiousness is varying with
  - time since infection,
  - age,
  - infectiousness is 2X greater in symptomatic persons (rate of moderate to asymptomatic infection 30%)
- Susceptibility is varying with
  - age



Treanor JJ, et al. *Textbook of influenza*. 1998. 517 Cauchemez et al. *Stat Med* 2004;23:3469

Population

- Demographics based on french national data
- Households fully-connected, other places as « scale-free » random graphs within districts
- Contacts :
  - Every day : Households
  - Working days : within School/Workplace/Nursing Home



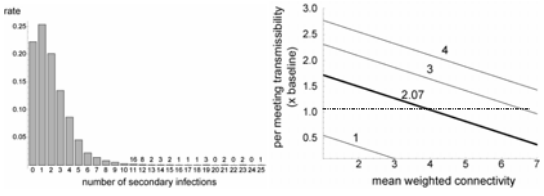
Barabasi et al. *Science* 1999;286:509 Albert et al. *Nature* 1999;401:130 Eubank S et al; *Nature* 2004;429:10

Baseline scenario

- Assumptions
  - No herd immunity
  - 80% of adult population working, 10% institutionalized elderly
  - 70% illness (i.e. detected) / 90% seeking medical advice / physician visit on first day of illness 40%, on second day 30%, after the second day 30%
  - 80% of detected individuals comply with confinment to the house (7 days)
- Empirical calibration of parameters (to fit plausible pandemic attack-rates)

Basic reproductive number R0

- Empirical Distribution (R0= 2.07)



- **In 22% simulations, no secondary case**
- **Mean generation time : 2.4 jrs**

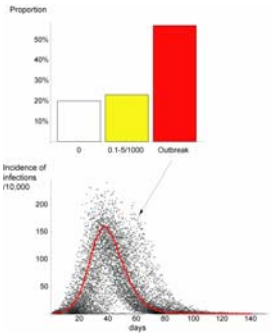
Anderson H; *Ann Appl Prob* 1998;8:1331

Baseline scenario

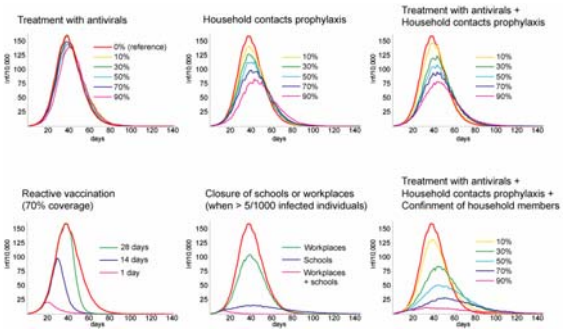
Cumulative numbers (per 100)

	Mean	Minimum-Maximum
Infections		
Total	**46.8**	**42.3 – 50.5**
Children (0-18 years)*	*76.5*	*71.9 –79.7*
*Adults (19-65 years)**	*39.9*	*34.8 – 44.0*
*Elderly (>65 years)**	*25.3*	*20.8– 30.1*
Physician visits	**31.2**	**28.0– 33.7**
Hospital admissions	**1.74**	**1.30-2.30**
Deaths	**0.36**	**0.17 – 0.55**
Lost workdays†	**137**	**118-150**

*per 100 individuals of a given age †per 100 working adults



Epidemic size (>5/1000)



User interface